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[Continued on next page]

(54) Title: PEPTIDES AND RELATED MOLECULES THAT BIND TO TALL-1

$a^1a^2a^3CDa^6La^8a^9a^{10}Ca^{12}a^{13}a^{14}$

(SEQ. ID. NO: 100),

$b^1b^2b^3Cb^5b^6Db^8Lb^{10}b^{11}b^{12}b^{13}b^{14}Cb^{16}b^{17}b^{18}$

(SEQ. ID. NO: 104)

$c^1c^2c^3Cc^5Dc^7Lc^9c^{10}c^{11}c^{12}c^{13}c^{14}Cc^{16}c^{17}c^{18}$

(SEQ. ID. NO: 105)

$d^1d^2d^3Cd^5d^6d^7WDd^{10}Ld^{13}d^{14}d^{15}Cd^{16}d^{17}d^{18}$

(SEQ. ID. NO: 106)

$e^1e^2e^3Ce^5e^6e^7De^9Le^{11}Ke^{13}Ce^{15}e^{16}e^{17}e^{18}$

(SEQ. ID. NO: 107)

$f^1f^2f^3Kf^5Df^7Lf^9f^{10}Qf^{12}f^{13}f^{14}$

(SEQ. ID NO: 109)

$(X^1)_s-V^1-(X^2)_b \quad (I)$

(57) Abstract: The present invention concerns therapeutic agents that modulate the activity of TALL-1. In accordance with the present invention, modulators of TALL-1 may comprise an amino acid sequence  $Dz^2Lz^4$  wherein  $z^2$  is an amino acid residue and  $z^4$  is threonyl or isoleucyl. Exemplary molecules comprise a sequence of the formulae  $a^1a^2a^3CDa^6La^8a^9a^{10}Ca^{12}a^{13}a^{14}$  (SEQ.ID.NO:100),  $b^1b^2b^3Cb^5b^6Db^8Lb^{10}b^{11}b^{12}b^{13}b^{14}Cb^{16}b^{17}b^{18}$  (SEQ.ID.NO:104),  $c^1c^2c^3Cc^5Dc^7Lc^9c^{10}c^{11}c^{12}c^{13}c^{14}Cc^{16}c^{17}c^{18}$  (SEQ.ID.NO:105),  $d^1d^2d^3Cd^5d^6d^7WDd^{10}Ld^{13}d^{14}d^{15}Cd^{16}d^{17}d^{18}$  (SEQ.ID.NO:106),  $e^1e^2e^3Ce^5e^6e^7De^9Le^{11}Ke^{13}Ce^{15}e^{16}e^{17}e^{18}$  (SEQ.ID.NO:107),  $f^1f^2f^3Kf^5Df^7Lf^9f^{10}Qf^{12}f^{13}f^{14}$  (SEQ.ID NO:109) wherein the substituents are as defined in the specification. The invention further comprises compositions of matter of the formula  $(X^1)_s-V^1-(X^2)_b$  wherein  $V^1$  is a vehicle that is covalently attached to one or more of the above TALL-1 modulating compositions of matter. The vehicle and the TALL-1 modulating composition of matter may be linked through the N- or C-terminus of the TALL-1 modulating portion. The preferred vehicle is an Fc domain, and the preferred Fc domain is an IgG Fc domain.

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## PEPTIDES AND RELATED MOLECULES THAT BIND TO TALL-1

This application is related to U.S. provisional application no. 60/290,196,  
5 filed May 11, 2001, which is hereby incorporated by reference.

### Background of the Invention

After years of study in necrosis of tumors, tumor necrosis factors (TNFs)  $\alpha$  and  $\beta$  were finally cloned in 1984. The ensuing years witnessed  
10 the emergence of a superfamily of TNF cytokines, including fas ligand (FasL), CD27 ligand (CD27L), CD30 ligand (CD30L), CD40 ligand (CD40L), TNF-related apoptosis-inducing ligand (TRAIL, also designated AGP-1), osteoprotegerin binding protein (OPG-BP or OPG ligand), 4-1BB ligand, LIGHT, APRIL, and TALL-1. Smith *et al.* (1994), *Cell* 76: 959-962;  
15 Lacey *et al.* (1998), *Cell* 93: 165-176; Chichepotiche *et al.* (1997), *J. Biol. Chem.* 272: 32401-32410; Mauri *et al.* (1998), *Immunity* 8: 21-30; Hahne *et al.* (1998), *J. Exp. Med.* 188: 1185-90; Shu *et al.* (1999), *J. Leukocyte Biology* 65: 680-3. This family is unified by its structure, particularly at the C-terminus. In addition, most members known to date are expressed in  
20 immune compartments, although some members are also expressed in other tissues or organs, as well. Smith *et al.* (1994), *Cell* 76: 959-62. All ligand members, with the exception of LT- $\alpha$ , are type II transmembrane proteins, characterized by a conserved 150 amino acid region within C-terminal extracellular domain. Though restricted to only 20-25% identity,  
25 the conserved 150 amino acid domain folds into a characteristic  $\beta$ -pleated sheet sandwich and trimerizes. This conserved region can be proteolytically released, thus generating a soluble functional form. Banner *et al.* (1993), *Cell* 73: 431-445.

Many members within this ligand family are expressed in lymphoid enriched tissues and play important roles in the immune system development and modulation. Smith *et al.* (1994). For example, TNF $\alpha$  is mainly synthesized by macrophages and is an important mediator for inflammatory responses and immune defenses. Tracey & Cerami (1994), *Ann. Rev. Med.* 45: 491-503. Fas-L, predominantly expressed in activated T cell, modulates TCR-mediated apoptosis of thymocytes. Nagata, S. & Suda, T. (1995) *Immunology Today* 16: 39-43; Castrim *et al.* (1996), *Immunity* 5: 617-27. CD40L, also expressed by activated T cells, provides an essential signal for B cell survival, proliferation and immunoglobulin isotype switching. Noelle (1996), *Immunity* 4: 415-9.

The cognate receptors for most of the TNF ligand family members have been identified. These receptors share characteristic multiple cysteine-rich repeats within their extracellular domains, and do not possess catalytic motifs within cytoplasmic regions. Smith *et al.* (1994). The receptors signal through direct interactions with death domain proteins (e.g. TRADD, FADD, and RIP) or with the TRAF proteins (e.g. TRAF2, TRAF3, TRAF5, and TRAF6), triggering divergent and overlapping signaling pathways, e.g. apoptosis, NF- $\kappa$ B activation, or JNK activation. Wallach *et al.* (1999), *Annual Review of Immunology* 17: 331-67. These signaling events lead to cell death, proliferation, activation or differentiation. The expression profile of each receptor member varies. For example, TNFR1 is expressed on a broad spectrum of tissues and cells, whereas the cell surface receptor of OPGL is mainly restricted to the osteoclasts. Hsu *et al.* (1999) *Proc. Natl. Acad. Sci. USA* 96: 3540-5.

A number of research groups have recently identified TNF family ligands with the same or substantially similar sequence. The ligand has been variously named neutrokin  $\alpha$  (WO 98/18921, published May 7, 1998), 63954 (WO 98/27114, published June 25, 1998), TL5 (EP 869 180, published October 7, 1998), NTN-2 (WO 98/55620 and WO 98/55621,



published December 10, 1998), TNRL1-alpha (WO 9911791, published March 11, 1999), kay ligand (WO99/12964, published March 18, 1999), and AGP-3 (U.S. Prov. App. Nos. 60/119,906, filed February 12, 1999 and 60/166,271, filed November 18, 1999, respectively); and TALL-1 (WO  
5 00/68378, published Nov. 16, 2000). Each of these references is hereby incorporated by reference. Hereinafter, the ligands reported therein are collectively referred to as TALL-1.

TALL-1 is a member of the TNF ligand superfamily that is functionally involved in B cell survival and proliferation. Transgenic mice  
10 overexpressing TALL-1 had severe B cell hyperplasia and lupus-like autoimmune disease. Khare *et al.* (2000) PNAS 97(7):3370-3375). Both TACI and BCMA serve as cell surface receptors for TALL-1. Gross *et al.* (2000), Nature 404: 995-999; Ware (2000), *J. Exp. Med.* 192(11): F35-F37; Ware (2000), Nature 404: 949-950; Xia *et al.* (2000), *J. Exp. Med.* 192(1):137-  
15 143; Yu *et al.* (2000), Nature Immunology 1(3):252-256; Marsters *et al.* (2000), Current Biology 10:785-788; Hatzoglou *et al.* (2000) *J. of Immunology* 165:1322-1330; Shu *et al.* (2000) PNAS 97(16):9156-9161; Thompson *et al.* (2000) *J. Exp. Med.* 192(1):129-135; Mukhopadhyay *et al.* (1999) *J. Biol. Chem.* 274(23): 15978-81; Shu *et al.* (1999) *J. Leukocyte Biol.*  
20 65:680-683; Gruss *et al.* (1995) Blood 85(12): 3378-3404; Smith *et al.* (1994), Cell 76: 959-962; U.S. Pat. No. 5,969,102, issued October 19, 1999; WO 00/67034, published November 9, 2000; WO 00/40716, published July 13, 2000; WO 99/35170, published July 15, 1999. Both receptors are expressed on B cells and signal through interaction with TRAF proteins. In addition,  
25 both TACI and BCMA also bind to another TNF ligand family member, APRIL. Yu *et al.* (2000), Nature Immunology 1(3) :252-256. APRIL has also been demonstrated to induce B cell proliferation.

To date, no recombinant or modified proteins employing peptide modulators of TALL-1 have been disclosed. Recombinant and modified

proteins are an emerging class of therapeutic agents. Useful modifications of protein therapeutic agents include combination with the "Fc" domain of an antibody and linkage to polymers such as polyethylene glycol (PEG) and dextran. Such modifications are discussed in detail in a patent  
5 application entitled, "Modified Peptides as Therapeutic Agents,"  
published WO 00/24782, which is hereby incorporated by reference in its entirety.

A much different approach to development of therapeutic agents is peptide library screening. The interaction of a protein ligand with its  
10 receptor often takes place at a relatively large interface. However, as  
demonstrated for human growth hormone and its receptor, only a few key residues at the interface contribute to most of the binding energy.  
Clackson *et al.* (1995), *Science* 267: 383-6. The bulk of the protein ligand  
merely displays the binding epitopes in the right topology or serves  
15 functions unrelated to binding. Thus, molecules of only "peptide" length  
(2 to 40 amino acids) can bind to the receptor protein of a given large  
protein ligand. Such peptides may mimic the bioactivity of the large  
protein ligand ("peptide agonists") or, through competitive binding,  
inhibit the bioactivity of the large protein ligand ("peptide antagonists").

20 Phage display peptide libraries have emerged as a powerful  
method in identifying such peptide agonists and antagonists. See, for  
example, Scott *et al.* (1990), *Science* 249: 386; Devlin *et al.* (1990), *Science*  
249: 404; U.S. Pat. No. 5,223,409, issued June 29, 1993; U.S. Pat. No.  
5,733,731, issued March 31, 1998; U.S. Pat. No. 5,498,530, issued March 12,  
25 1996; U.S. Pat. No. 5,432,018, issued July 11, 1995; U.S. Pat. No. 5,338,665,  
issued August 16, 1994; U.S. Pat. No. 5,922,545, issued July 13, 1999; WO  
96/40987, published December 19, 1996; and WO 98/15833, published  
April 16, 1998 (each of which is incorporated by reference in its entirety).  
In such libraries, random peptide sequences are displayed by fusion with

coat proteins of filamentous phage. Typically, the displayed peptides are affinity-eluted against an immobilized target protein. The retained phages may be enriched by successive rounds of affinity purification and repropagation. The best binding peptides may be sequenced to identify  
5 key residues within one or more structurally related families of peptides. See, e.g., Cwirla *et al.* (1997), *Science* 276: 1696-9, in which two distinct families were identified. The peptide sequences may also suggest which residues may be safely replaced by alanine scanning or by mutagenesis at the DNA level. Mutagenesis libraries may be created and screened to  
10 further optimize the sequence of the best binders. Lowman (1997), *Ann. Rev. Biophys. Biomol. Struct.* 26: 401-24.

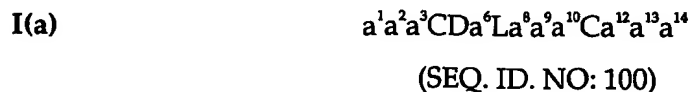
Structural analysis of protein-protein interaction may also be used to suggest peptides that mimic the binding activity of large protein ligands. In such an analysis, the crystal structure may suggest the identity  
15 and relative orientation of critical residues of the large protein ligand, from which a peptide may be designed. See, e.g., Takasaki *et al.* (1997), *Nature Biotech.* 15: 1266-70. These analytical methods may also be used to investigate the interaction between a receptor protein and peptides selected by phage display, which may suggest further modification of the  
20 peptides to increase binding affinity.

Other methods compete with phage display in peptide research. A peptide library can be fused to the carboxyl terminus of the *lac* repressor and expressed in *E. coli*. Another *E. coli*-based method allows display on the cell's outer membrane by fusion with a peptidoglycan-associated  
25 lipoprotein (PAL). Hereinafter, these and related methods are collectively referred to as "*E. coli* display." In another method, translation of random RNA is halted prior to ribosome release, resulting in a library of polypeptides with their associated RNA still attached. Hereinafter, this and related methods are collectively referred to as "ribosome display."

Other methods employ peptides linked to RNA; for example, PROfusion technology, Phylos, Inc. See, for example, Roberts & Szostak (1997), Proc. Natl. Acad. Sci. USA, 94: 12297-303. Hereinafter, this and related methods are collectively referred to as "RNA-peptide screening." Chemically  
 5 derived peptide libraries have been developed in which peptides are immobilized on stable, non-biological materials, such as polyethylene rods or solvent-permeable resins. Another chemically derived peptide library uses photolithography to scan peptides immobilized on glass slides. Hereinafter, these and related methods are collectively referred to as  
 10 "chemical-peptide screening." Chemical-peptide screening may be advantageous in that it allows use of D-amino acids and other unnatural analogues, as well as non-peptide elements. Both biological and chemical methods are reviewed in Wells & Lowman (1992), Curr. Opin. Biotechnol. 3: 355-62. Conceptually, one may discover peptide mimetics of any  
 15 protein using phage display, RNA-peptide screening, and the other methods mentioned above.

### Summary of the Invention

The present invention concerns therapeutic agents that modulate the activity of TALL-1. In accordance with the present invention,  
 20 modulators of TALL-1 may comprise an amino acid sequence  $Dz^2Lz^4$  (SEQ ID NO: 108) wherein  $z^2$  is an amino acid residue and  $z^4$  is threonyl or isoleucyl. Such modulators of TALL-1 comprise molecules of the following formulae:



wherein:

- $a^1, a^2, a^3$  are each independently absent or amino acid residues;
- $a^6$  is an amino acid residue;
- $a^9$  is a basic or hydrophobic residue;
- 30  $a^8$  is threonyl or isoleucyl;

a<sup>12</sup> is a neutral polar residue; and  
 a<sup>13</sup> and a<sup>14</sup> are each independently absent or amino acid residues.

I(b)  $b^1 b^2 b^3 C b^5 b^6 D b^8 L b^{10} b^{11} b^{12} b^{13} b^{14} C b^{16} b^{17} b^{18}$

5 (SEQ. ID. NO: 104)

wherein:

b<sup>1</sup> and b<sup>2</sup> are each independently absent or amino acid residues;  
 b<sup>3</sup> is an acidic or amide residue;  
 b<sup>5</sup> is an amino acid residue;  
 10 b<sup>6</sup> is an aromatic residue;  
 b<sup>8</sup> is an amino acid residue;  
 b<sup>10</sup> is T or I;  
 b<sup>11</sup> is a basic residue;  
 b<sup>12</sup> and b<sup>13</sup> are each independently amino acid residues;  
 15 b<sup>14</sup> is a neutral polar residue; and  
 b<sup>16</sup>, b<sup>17</sup>, and b<sup>18</sup> are each independently absent or amino acid  
 residues.

I(c)  $c^1 c^2 c^3 C c^5 D c^7 L c^9 c^{10} c^{11} c^{12} c^{13} c^{14} C c^{16} c^{17} c^{18}$

(SEQ. ID. NO:105)

20 wherein:

c<sup>1</sup>, c<sup>2</sup>, and c<sup>3</sup> are each independently absent or amino acid residues;  
 c<sup>5</sup> is an amino acid residue;  
 c<sup>7</sup> is an amino acid residue;  
 c<sup>9</sup> is T or I;  
 25 c<sup>10</sup> is a basic residue;  
 c<sup>11</sup> and c<sup>12</sup> are each independently amino acid residues;  
 c<sup>13</sup> is a neutral polar residue;  
 c<sup>14</sup> is an amino acid residue;  
 c<sup>16</sup> is an amino acid residue;

c<sup>17</sup> is a neutral polar residue; and

c<sup>18</sup> is an amino acid residue or is absent.

I(d) d<sup>1</sup>d<sup>2</sup>d<sup>3</sup>Cd<sup>5</sup>d<sup>6</sup>d<sup>7</sup>WDd<sup>10</sup>Ld<sup>12</sup>d<sup>13</sup>d<sup>14</sup>Cd<sup>15</sup>d<sup>16</sup>d<sup>17</sup>

(SEQ. ID. NO: 106)

5 wherein:

d<sup>1</sup>, d<sup>2</sup>, and d<sup>3</sup> are each independently absent or amino acid residues;

d<sup>5</sup>, d<sup>6</sup>, and d<sup>7</sup> are each independently amino acid residues;

d<sup>10</sup> is an amino acid residue;

d<sup>13</sup> is T or I;

10 d<sup>14</sup> is an amino acid residue; and

d<sup>16</sup>, d<sup>17</sup>, and d<sup>18</sup> are each independently absent or amino acid residues.

I(e) e<sup>1</sup>e<sup>2</sup>e<sup>3</sup>Ce<sup>5</sup>e<sup>6</sup>e<sup>7</sup>De<sup>9</sup>Le<sup>11</sup>Ke<sup>13</sup>Ce<sup>15</sup>e<sup>16</sup>e<sup>17</sup>e<sup>18</sup>

(SEQ. ID. NO: 107)

15 wherein:

e<sup>1</sup>, e<sup>2</sup>, and e<sup>3</sup> are each independently absent or amino acid residues;

e<sup>5</sup>, e<sup>6</sup>, e<sup>7</sup>, e<sup>9</sup>, and e<sup>13</sup> are each independently amino acid residues;

e<sup>11</sup> is T or I; and

e<sup>15</sup>, e<sup>16</sup>, and e<sup>17</sup> are each independently absent or amino acid residues.

20 I(f) f<sup>1</sup>f<sup>2</sup>f<sup>3</sup>Kf<sup>5</sup>Df<sup>7</sup>Lf<sup>9</sup>f<sup>10</sup>Qf<sup>12</sup>f<sup>13</sup>f<sup>14</sup>

(SEQ. ID NO: 109)

wherein:

f<sup>1</sup>, f<sup>2</sup>, and f<sup>3</sup> are absent or are amino acid residues (with one of f<sup>1</sup>, f<sup>2</sup>,

and f<sup>3</sup> preferred to be C when one of f<sup>12</sup>, f<sup>13</sup>, and f<sup>14</sup> is C);

25 f<sup>5</sup> is W, Y, or F (W preferred);

f<sup>7</sup> is an amino acid residue (L preferred);

f<sup>9</sup> is T or I (T preferred);

f<sup>10</sup> is K, R, or H (K preferred);

$f^{12}$  is C, a neutral polar residue, or a basic residue (W, C, or R preferred);

$f^{13}$  is C, a neutral polar residue or is absent (V preferred); and

5  $f^{14}$  is any amino acid residue or is absent;  
provided that only one of  $f^1$ ,  $f^2$ , and  $f^3$  may be C, and only one of  $f^{12}$ ,  $f^{13}$ , and  $f^{14}$  may be C.

Compounds of formulae I(a) through I(f) above incorporate Dz<sup>2</sup>Lz<sup>4</sup>, as well as SEQ ID NO: 63 hereinafter. The sequence of I(f) was derived as  
10 a consensus sequence as described in Example 1 hereinbelow. Of compounds within formula I(f), those within the formula

**I(f')**  $f^1 f^2 f^3 K W D f^7 L f^8 K Q f^{12} f^{13} f^{14}$   
(SEQ ID NO: 125)

are preferred. Compounds falling within formula I(f') include SEQ ID  
15 NOS: 32, 58, 60, 62, 63, 66, 67, 69, 70, 114, 115, 122, 123, 124, 147-150, 152-177, 179, 180, 187.

Also in accordance with the present invention are compounds having the consensus motif:

**PFPWE**  
20 (SEQ ID NO: 110)

which also bind TALL-1.

Further in accordance with the present invention are compounds of the formulae:

**I(g)**  $g^1 g^2 g^3 C g^5 P F g^8 W g^{10} C g^{11} g^{12} g^{13}$   
25 (SEQ. ID. NO. 101)

wherein:

$g^1$ ,  $g^2$  and  $g^3$  are each independently absent or amino acid residues;  
 $g^5$  is a neutral polar residue;  
 $g^8$  is a neutral polar residue;  
30  $g^{10}$  is an acidic residue;

$g^{12}$  and  $g^{13}$  are each independently amino acid residues; and  
 $g^{14}$  is absent or is an amino acid residue.

**I(h)**  $h^1 h^2 h^3 C W h^6 h^7 W G h^{10} C h^{12} h^{13} h^{14}$   
 (SEQ. ID. NO: 102)

5 wherein:

$h^1$ ,  $h^2$ , and  $h^3$  are each independently absent or amino acid residues;  
 $h^6$  is a hydrophobic residue;  
 $h^7$  is a hydrophobic residue;  
 $h^{10}$  is an acidic or polar hydrophobic residue; and  
 10  $h^{12}$ ,  $h^{13}$ , and  $h^{14}$  are each independently absent or amino acid residues.

**I(i)**  $i^{1,2,3} C i^{4,5,6,7,8,9,10} C i^{12,13,14}$   
 (SEQ. ID. NO: 103)

wherein:

$i^1$  is absent or is an amino acid residue;  
 15  $i^2$  is a neutral polar residue;  
 $i^3$  is an amino acid residue;  
 $i^5$ ,  $i^6$ ,  $i^7$ , and  $i^8$  are each independently amino acid residues;  
 $i^9$  is an acidic residue;  
 $i^{10}$  is an amino acid residue;  
 20  $i^{12}$  and  $i^{13}$  are each independently amino acid residues; and  
 $i^{14}$  is a neutral polar residue.

The compounds defined by formulae I(g) through I(i) also bind  
 TALL-1.

Further in accordance with the present invention, modulators of  
 25 TALL-1 comprise:

a) a TALL-1 modulating domain (e.g., an amino acid sequence  
 of Formulae I(a) through I(i)), preferably the amino acid  
 sequence  $Dz^2Lz^4$ , or sequences derived therefrom by phage  
 display, RNA-peptide screening, or the other techniques  
 30 mentioned above; and



- b) a vehicle, such as a polymer (e.g., PEG or dextran) or an Fc domain, which is preferred;

wherein the vehicle is covalently attached to the TALL-1 modulating domain. The vehicle and the TALL-1 modulating domain may be linked through the N- or C-terminus of the TALL-1 modulating domain, as described further below. The preferred vehicle is an Fc domain, and the preferred Fc domain is an IgG Fc domain. Such Fc-linked peptides are referred to herein as "peptibodies." Preferred TALL-1 modulating domains comprise the amino acid sequences described hereinafter in Tables 1 and 2. Other TALL-1 modulating domains can be generated by phage display, RNA-peptide screening and the other techniques mentioned herein.

Further in accordance with the present invention is a process for making TALL-1 modulators, which comprises:

- a. selecting at least one peptide that binds to TALL-1 ; and  
b. covalently linking said peptide to a vehicle.

The preferred vehicle is an Fc domain. Step (a) is preferably carried out by selection from the peptide sequences in Table 2 hereinafter or from phage display, RNA-peptide screening, or the other techniques mentioned herein.

The compounds of this invention may be prepared by standard synthetic methods, recombinant DNA techniques, or any other methods of preparing peptides and fusion proteins. Compounds of this invention that encompass non-peptide portions may be synthesized by standard organic chemistry reactions, in addition to standard peptide chemistry reactions when applicable.

The primary use contemplated for the compounds of this invention is as therapeutic or prophylactic agents. The vehicle-linked peptide may

have activity comparable to—or even greater than—the natural ligand mimicked by the peptide.

The compounds of this invention may be used for therapeutic or prophylactic purposes by formulating them with appropriate pharmaceutical carrier materials and administering an effective amount to a patient, such as a human (or other mammal) in need thereof. Other related aspects are also included in the instant invention.

Numerous additional aspects and advantages of the present invention will become apparent upon consideration of the figures and detailed description of the invention.

### **Brief Description of the Figures**

Figure 1 shows exemplary Fc dimers that may be derived from an IgG1 antibody. "Fc" in the figure represents any of the Fc variants within the meaning of "Fc domain" herein. "X<sup>1</sup>" and "X<sup>2</sup>" represent peptides or linker-peptide combinations as defined hereinafter. The specific dimers are as follows:

A, D: Single disulfide-bonded dimers. IgG1 antibodies typically have two disulfide bonds at the hinge region of the antibody. The Fc domain in Figures 1A and 1D may be formed by truncation between the two disulfide bond sites or by substitution of a cysteinyl residue with an unreactive residue (e.g., alanyl). In Figure 1A, the Fc domain is linked at the amino terminus of the peptides; in 1D, at the carboxyl terminus.

B, E: Doubly disulfide-bonded dimers. This Fc domain may be formed by truncation of the parent antibody to retain both cysteinyl residues in the Fc domain chains or by expression from a construct including a sequence encoding such an Fc domain. In Figure 1B, the Fc domain is linked at the amino terminus of the peptides; in 1E, at the carboxyl terminus.

C, F: Noncovalent dimers. This Fc domain may be formed by elimination of the cysteinyl residues by either truncation or substitution. One may desire to eliminate the cysteinyl residues to avoid impurities formed by reaction of the cysteinyl residue with cysteinyl residues of other proteins present in the host cell. The noncovalent bonding of the Fc domains is sufficient to hold together the dimer. Other dimers may be formed by using Fc domains derived from different types of antibodies (e.g., IgG2, IgM).

Figure 2 shows the structure of preferred compounds of the invention that feature tandem repeats of the pharmacologically active peptide. Figure 2A shows a single chain molecule and may also represent the DNA construct for the molecule. Figure 2B shows a dimer in which the linker-peptide portion is present on only one chain of the dimer. Figure 2C shows a dimer having the peptide portion on both chains. The dimer of Figure 2C will form spontaneously in certain host cells upon expression of a DNA construct encoding the single chain shown in Figure 3A. In other host cells, the cells could be placed in conditions favoring formation of dimers or the dimers can be formed in vitro.

Figure 3 shows exemplary nucleic acid and amino acid sequences (SEQ ID NOS: 1 and 2, respectively) of human IgG1 Fc that may be used in this invention.

Figures 4A through 4F show the nucleotide and amino acid sequences (SEQ ID NOS: 3-27) S of NdeI to SalI fragments encoding peptide and linker.

Figures 5A through 5M show the nucleotide sequence (SEQ ID NO: 28) of pAMG21-RANK-Fc vector, which was used to construct Fc-linked molecules of the present invention. These figures identify a number of features of the nucleic acid, including:

- promoter regions PcopB, PrepA, RNAI, APHII, luxPR, and luxPL;
- mRNA for APHII, luxR;

- coding sequences and amino acid sequences for the proteins copB protein, copT, repAI, repA4, APHII, luxR, RANK, and Fc;
- binding sites for the proteins copB, CRP;
- hairpins T1, T2, T7, and toop;
- 5 • operator site for lux protein;
- enzyme restriction sites for PfIII08I, BglII, ScaI, BmnI, DrdII, DraIII, BstBI, AceIII, AflII, PfiMI, BglI, SfiI, BstEII, BspLulII, NspV, BplI, EagI, BcgI, NsiI, BsaI, Pspl406I, AatII, BsmI, NruI, NdeI, ApaLI, Acc65I, KpnI, SalI, AccI, BspEI, AhdI, BspHI, EcoNI, BsrGI, BmaI, SmaI, SexAI, BamHI, and BlpI.

10        Figures 6A and 6B show the DNA sequence (SEQ ID NO: 97) inserted into pCFM1656 between the unique AatII (position #4364 in pCFM1656) and SacII (position #4585 in pCFM1656) restriction sites to form expression plasmid pAMG21 (ATCC accession no. 98113).

Figure 7 shows that the TALL-1 peptibody (SEQ ID NO: 70) inhibits  
 15 TALL-1-mediated B cell proliferation. Purified B cells ( $10^5$ ) from B6 mice were cultured in triplicates in 96-well plated with the indicated amounts of TALL-1 consensus peptibody in the presence of 10 ng/ml TALL-1 plus 2  $\mu$ g/ml anti-IgM antibody. Proliferation was measured by radioactive [ $^3$ H]thymidine uptake in the last 18h of pulse. Data shown represent mean  $\pm$  SD triplicate wells.

20        Figure 8 shows that a TALL-1 N-terminal tandem dimer peptibodies (SEQ ID NO: 123, 124 in Table 5B hereinafter) are preferable for inhibition of TALL-1-mediated B cell proliferation. Purified B cells ( $10^5$ ) from B6 mice were cultured in triplicates in 96-well plated with the indicated amounts of TALL-1 12-3 peptibody and TALL-1 consensus peptibody (SEQ ID NOS: 115 and 122 of Table 5B) or the  
 25 related dimer peptibodies (SEQ ID NOS: 123, 124) in the presence of 10 ng/ml TALL-1 plus 2  $\mu$ g/ml anti-IgM antibody. Proliferation was measured by radioactive [ $^3$ H]thymidine uptake in the last 18h of pulse. Data shown represent mean  $\pm$  SD triplicate wells.

Figure 9. AGP3 peptibody binds to AGP3 with high affinity.  
 30        Dissociation equilibrium constant ( $K_D$ ) was obtained from nonlinear regression

of the competition curves using a dual-curve one-site homogeneous binding model (KinEx™ software).  $K_D$  is about 4 pM for AGP3 peptibody binding with human AGP3 (SEQ ID NO: 123).

Figures 10A and 10B. AGP3 peptibody blocks both human and  
5 murine AGP3 in the Biacore competition assay. Soluble human TACI protein was immobilized to B1 chip. 1 nM of recombinant human AGP3 protein (upper panel) or 5 nM of recombinant murine AGP3 protein (lower panel) was incubated with indicated amount of AGP3 peptibody before injected over the surface of receptor. Relative human AGP3 and murine AGP3 (binding response was shown  
10 (SEQ ID NO: 123).

Figures 11A and 11B. AGP3 peptibody blocked AGP3 binding to all three receptors TACI, BCMA and BAFFR in Biacore competition assay. Recombinant soluble receptor TACI, BCMA and BAFFR proteins were immobilized to CM5 chip. 1 nM of recombinant human AGP3 (upper panel) were  
15 incubated with indicated amount of AGP3 peptibody before injected over each receptor surface. Relative binding of AGP3 was measured. Similarly, 1 nM of recombinant APRIL protein was incubated with indicated amount of AGP3 peptibody before injected over each receptor surface. AGP3 peptibody didn't inhibit APRIL binding to all three receptors (SEQ ID NO: 123).

Figures 12A and 12B. AGP3 peptibody inhibits mouse serum  
20 immunoglobulin level increase induced by human AGP3 challenge. Balb/c mice received 7 daily intraperitoneal injections of 1 mg/Kg human AGP3 protein along with saline, human Fc, or AGP3 peptibody at indicated doses, and were bled on day 8. Serum total IgM and IgA level were measured by ELISA (SEQ ID NO:  
25 123).

Figure 13. AGP3 peptibody treatment reduced arthritis severity in the mouse CIA model. Eight to 12 weeks old DBA/1 male mice were immunized with bovine collagen type II (bCII) emulsified in complete freunds adjuvant intradermally at the base of tail, and were boosted 3 weeks after the initial  
30 immunization with bCII emulsified in incomplete freunds adjuvant. Treatment with indicated dosage of AGP3 peptibody was begun from the day of booster

immunization for 4 weeks. As described before (Khare et al., *J. Immunol.* 155: 3653-9, 1995), all four paws were individually scored from 0-3 for arthritis severity (SEQ ID NO: 123).

Figure 14. AGP3 peptibody treatment inhibited anti-collagen antibody generation in the mouse CIA model. Serum samples were taken one week after final treatment (day 35) as described above. Serum anti-collagen II antibody level was determined by ELISA analysis (SEQ ID NO: 123).

Figures 15A and 15B. AGP3 peptibody treatment delayed proteinuria onset and improved survival in NZB/NZW lupus mice. Five-month-old lupus prone NZBx NZBWF1 mice were treated i.p. 3X/week for 8 weeks with PBS or indicated doses of AGP3 peptibody (SEQ ID NO: 123) or human Fc proteins. Protein in the urine was evaluated monthly throughout the life of the experiment with Albustix reagent strips (Bayer AG).

Figures 16A and 16B show the nucleic acid and amino acid sequences of a preferred TALL-1-binding peptibody (SEQ ID NOS: 189 and 123)

## Detailed Description of the Invention

### Definition of Terms

The terms used throughout this specification are defined as follows, unless otherwise limited in specific instances.

#### General definitions

The term "comprising" means that a compound may include additional amino acids on either or both of the N- or C- termini of the given sequence. Of course, these additional amino acids should not significantly interfere with the activity of the compound.

Additionally, physiologically acceptable salts of the compounds of this invention are also encompassed herein. The term "physiologically acceptable salts" refers to any salts that are known or later discovered to be pharmaceutically acceptable. Some specific examples are: acetate;

trifluoroacetate; hydrohalides, such as hydrochloride and hydrobromide; sulfate; citrate; tartrate; glycolate; and oxalate.

#### Amino acids

The term "acidic residue" refers to amino acid residues in D- or L-form having sidechains comprising acidic groups. Exemplary acidic residues include D and E.

The term "amide residue" refers to amino acids in D- or L-form having sidechains comprising amide derivatives of acidic groups. Exemplary residues include N and Q.

10 The term "aromatic residue" refers to amino acid residues in D- or L-form having sidechains comprising aromatic groups. Exemplary aromatic residues include F, Y, and W.

The term "basic residue" refers to amino acid residues in D- or L-form having sidechains comprising basic groups. Exemplary basic residues include H, K, and R.

The term "hydrophilic residue" refers to amino acid residues in D- or L-form having sidechains comprising polar groups. Exemplary hydrophilic residues include C, S, T, N, and Q.

20 The term "nonfunctional residue" refers to amino acid residues in D- or L-form having sidechains that lack acidic, basic, or aromatic groups. Exemplary nonfunctional amino acid residues include M, G, A, V, I, L and norleucine (Nle).

The term "neutral polar residue" refers to amino acid residues in D- or L-form having sidechains that lack basic, acidic, or polar groups. Exemplary neutral polar amino acid residues include A, V, L, I, P, W, M, and F.

The term "polar hydrophobic residue" refers to amino acid residues in D- or L-form having sidechains comprising polar groups. Exemplary polar hydrophobic amino acid residues include T, G, S, Y, C, Q, and N.

The term "hydrophobic residue" refers to amino acid residues in D- or L-form having sidechains that lack basic or acidic groups. Exemplary hydrophobic amino acid residues include A, V, L, I, P, W, M, F, T, G, S, Y, C, Q, and N.

5        Peptides

The term "peptide" refers to molecules of 1 to 40 amino acids, with molecules of 5 to 20 amino acids preferred. Exemplary peptides may comprise the TALL-1 modulating domain of a naturally occurring molecule or comprise randomized sequences.

10        The term "randomized" as used to refer to peptide sequences refers to fully random sequences (e.g., selected by phage display methods or RNA-peptide screening) and sequences in which one or more residues of a naturally occurring molecule is replaced by an amino acid residue not appearing in that position in the naturally occurring molecule. Exemplary  
15        methods for identifying peptide sequences include phage display, *E. coli* display, ribosome display, RNA-peptide screening, chemical screening, and the like.

The term "TALL-1 modulating domain" refers to any amino acid sequence that binds to the TALL-1 and comprises naturally occurring  
20        sequences or randomized sequences. Exemplary TALL-1 modulating domains can be identified or derived by phage display or other methods mentioned herein.

The term "TALL-1 antagonist" refers to a molecule that binds to the TALL-1 and increases or decreases one or more assay parameters opposite  
25        from the effect on those parameters by full length native TALL-1. Such activity can be determined, for example, by such assays as described in the subsection entitled "Biological activity of AGP-3" in the Materials & Methods section of the patent application entitled, "TNF-RELATED PROTEINS", WO 00/47740, published August 17, 2000.



### Vehicles and peptibodies

The term "vehicle" refers to a molecule that prevents degradation  
5 and/or increases half-life, reduces toxicity, reduces immunogenicity, or  
increases biological activity of a therapeutic protein. Exemplary vehicles  
include an Fc domain (which is preferred) as well as a linear polymer (e.g.,  
polyethylene glycol (PEG), polylysine, dextran, etc.); a branched-chain  
polymer (see, for example, U.S. Patent No. 4,289,872 to Denkenwalter et  
10 al., issued September 15, 1981; 5,229,490 to Tam, issued July 20, 1993; WO  
93/21259 by Frechet et al., published 28 October 1993); a lipid; a  
cholesterol group (such as a steroid); a carbohydrate or oligosaccharide  
(e.g., dextran); any natural or synthetic protein, polypeptide or peptide  
that binds to a salvage receptor; albumin, including human serum  
15 albumin (HSA), leucine zipper domain, and other such proteins and  
protein fragments. Vehicles are further described hereinafter.

The term "native Fc" refers to molecule or sequence comprising the  
sequence of a non-antigen-binding fragment resulting from digestion of  
whole antibody, whether in monomeric or multimeric form. The original  
20 immunoglobulin source of the native Fc is preferably of human origin and  
may be any of the immunoglobulins, although IgG1 and IgG2 are  
preferred. Native Fc's are made up of monomeric polypeptides that may  
be linked into dimeric or multimeric forms by covalent (i.e., disulfide  
bonds) and non-covalent association. The number of intermolecular  
25 disulfide bonds between monomeric subunits of native Fc molecules  
ranges from 1 to 4 depending on class (e.g., IgG, IgA, IgE) or subclass (e.g.,  
IgG1, IgG2, IgG3, IgA1, IgGA2). One example of a native Fc is a disulfide-  
bonded dimer resulting from papain digestion of an IgG (see Ellison et al.

(1982), Nucleic Acids Res. 10: 4071-9). The term "native Fc" as used herein is generic to the monomeric, dimeric, and multimeric forms.

The term "Fc variant" refers to a molecule or sequence that is modified from a native Fc but still comprises a binding site for the salvage  
5 receptor, FcRn. International applications WO 97/34631 (published 25 September 1997) and WO 96/32478 describe exemplary Fc variants, as well as interaction with the salvage receptor, and are hereby incorporated by reference in their entirety. Thus, the term "Fc variant" comprises a molecule or sequence that is humanized from a non-human native Fc.  
10 Furthermore, a native Fc comprises sites that may be removed because they provide structural features or biological activity that are not required for the fusion molecules of the present invention. Thus, the term "Fc variant" comprises a molecule or sequence that lacks one or more native Fc sites or residues that affect or are involved in (1) disulfide bond  
15 formation, (2) incompatibility with a selected host cell (3) N-terminal heterogeneity upon expression in a selected host cell, (4) glycosylation, (5) interaction with complement, (6) binding to an Fc receptor other than a salvage receptor, or (7) antibody-dependent cellular cytotoxicity (ADCC). Fc variants are described in further detail hereinafter.

20 The term "Fc domain" encompasses native Fc and Fc variant molecules and sequences as defined above. As with Fc variants and native Fc's, the term "Fc domain" includes molecules in monomeric or multimeric form, whether digested from whole antibody or produced by other means.

25 The term "multimer" as applied to Fc domains or molecules comprising Fc domains refers to molecules having two or more polypeptide chains associated covalently, noncovalently, or by both covalent and non-covalent interactions. IgG molecules typically form dimers; IgM, pentamers; IgD, dimers; and IgA, monomers, dimers,

trimers, or tetramers. Multimers may be formed by exploiting the sequence and resulting activity of the native Ig source of the Fc or by derivatizing (as defined below) such a native Fc.

The term "dimer" as applied to Fc domains or molecules  
5 comprising Fc domains refers to molecules having two polypeptide chains associated covalently or non-covalently. Thus, exemplary dimers within the scope of this invention are as shown in Figure 1.

The terms "derivatizing" and "derivative" or "derivatized" comprise processes and resulting compounds respectively in which (1) the  
10 compound has a cyclic portion; for example, cross-linking between cysteinyl residues within the compound; (2) the compound is cross-linked or has a cross-linking site; for example, the compound has a cysteinyl residue and thus forms cross-linked dimers in culture or in vivo; (3) one or more peptidyl linkage is replaced by a non-peptidyl linkage; (4) the N-  
15 terminus is replaced by  $-NRR^1$ ,  $NRC(O)R^1$ ,  $-NRC(O)OR^1$ ,  $-NRS(O)_2R^1$ ,  $-NHC(O)NHR$ , a succinimide group, or substituted or unsubstituted benzyloxycarbonyl-NH-, wherein R and  $R^1$  and the ring substituents are as defined hereinafter; (5) the C-terminus is replaced by  $-C(O)R^2$  or  $-NR^3R^4$  wherein  $R^2$ ,  $R^3$  and  $R^4$  are as defined hereinafter; and (6) compounds in  
20 which individual amino acid moieties are modified through treatment with agents capable of reacting with selected side chains or terminal residues. Derivatives are further described hereinafter.

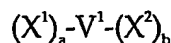
The terms "peptibody" and "peptibodies" refer to molecules comprising an Fc domain and at least one peptide. Such peptibodies may  
25 be multimers or dimers or fragments thereof, and they may be derivatized. In the present invention, the molecules of formulae II through VI hereinafter are peptibodies when  $V^1$  is an Fc domain.

## Structure of compounds

In General. The present inventors identified sequences capable of binding to and modulating the biological activity of TALL-1. These sequences can be modified through the techniques mentioned above  
 5 by which one or more amino acids may be changed while maintaining or even improving the binding affinity of the peptide.

In the compositions of matter prepared in accordance with this invention, the peptide(s) may be attached to the vehicle through the peptide's N-terminus or C-terminus. Any of these peptides may be linked  
 10 in tandem (i.e., sequentially), with or without linkers. Thus, the vehicle-peptide molecules of this invention may be described by the following formula:

II



15 wherein:

$V^1$  is a vehicle (preferably an Fc domain);

$X^1$  and  $X^2$  are each independently selected from  $-(L^1)_c-P^1$ ,  $-(L^1)_c-P^1-(L^2)_d-P^2$ ,  $-(L^1)_c-P^1-(L^2)_d-P^2-(L^3)_e-P^3$ , and  $-(L^1)_c-P^1-(L^2)_d-P^2-(L^3)_e-P^3-(L^4)_f-P^4$

$P^1$ ,  $P^2$ ,  $P^3$ , and  $P^4$  are each independently sequences of TALL-1  
 20 modulating domains, such as those of Formulae I(a) through I(i);

$L^1$ ,  $L^2$ ,  $L^3$ , and  $L^4$  are each independently linkers; and

$a$ ,  $b$ ,  $c$ ,  $d$ ,  $e$ , and  $f$  are each independently 0 or 1, provided that at least one of  $a$  and  $b$  is 1.

Thus, compound II comprises preferred compounds of the  
 25 formulae

III



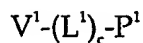
and multimers thereof wherein  $V^1$  is an Fc domain and is attached at the C-terminus of  $A^1$ ;

IV



and multimers thereof wherein  $V^1$  is an Fc domain and is attached at the N-terminus of  $A^2$ ;

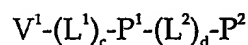
5 V



and multimers thereof wherein  $V^1$  is an Fc domain and is attached at the N-terminus of  $-(L^1)_c-P^1$ ; and

VI

10



and multimers thereof wherein  $V^1$  is an Fc domain and is attached at the N-terminus of  $-L^1-P^1-L^2-P^2$ .

Peptides. The peptides of this invention are useful as TALL-1 modulating peptides or as TALL-1 modulating domains in the molecules of formulae II through VI. Molecules of this invention comprising these peptide sequences may be prepared by methods known in the art.

Preferred peptide sequences are those of the foregoing formulae I(a) having the substituents identified below.

**Table 1--Preferred peptide substituents**

|              |  |
|--------------|--|
| Formula I(a) | $a^8$ is T;<br>$a^9$ is a basic residue (K most preferred); and<br>$a^{12}$ is a neutral polar residue (F most preferred). |
| Formula I(b) | $b^3$ is D, Q, or E;<br>$b^6$ is W or Y;<br>$b^{10}$ is T;<br>$b^{11}$ is K or R; and<br>$b^{14}$ is V or L.               |
| Formula I(c) | $c^9$ is T ;<br>$c^{10}$ is K or R;<br>$c^{13}$ is a I, L, or V; and<br>$c^{17}$ is A or L.                                |
| Formula I(d) | $d^{13}$ is T.   |
| Formula I(e) | $e^{11}$ is T.   |
| Formula I(f) | $f^6$ is T;<br>$f^7$ is K; and<br>$f^{10}$ is V.   |
| Formula I(g) | $g^5$ is W;<br>$g^8$ is P;<br>$g^{10}$ is E; and<br>$g^{13}$ is a basic residue.   |
| Formula I(h) | $h^1$ is G;<br>$h^6$ is A;<br>$h^7$ is a neutral polar residue; and<br>$h^{10}$ is an acidic residue.                      |
| Formula I(i) | $i^2$ is W; and<br>$i^{14}$ is W.  |

Preferred peptide sequences appear in Table 2 below.

Table 2—Preferred TALL-1 modulating domains

| Sequence           | SEQ ID NO: |
|--------------------|------------|
| PGTCFFFPWECTHA     | 29         |
| WGACWFPFWECFKE     | 30         |
| VPFCDLLTKHCFEA     | 31         |
| GSRCYKWDVLTQCFHH   | 32         |
| LPGCKWDLLIKQWVCDPL | 33         |
| SADCYFDILTKSDVCTSS | 34         |
| SDDCMYDQLTRMFICSNL | 35         |
| DLNCKYDELTYKEWCQFN | 36         |
| FHDCKYDLLTRQMVCHGL | 37         |
| RNHCFWDHLLKQDICPSP | 38         |
| ANQCWWDSTTKKNVCEFF | 39         |
| YKGRQWDDILTRSWVVS  | 126        |
| QDVGLWWDILTRAWMPNI | 127        |
| QNAQRVWDLIRTWVYPQ  | 128        |
| GWNEAWWDELTKIWVLEQ | 129        |
| RITCDTWDSLTKKCVQPS | 130        |
| GAIMQFWDSTTKTWLRQS | 131        |
| WLHSCWWDPLTKHWLQKV | 132        |
| SEWFFWFDPLTRAQLKFR | 133        |
| GVWFWWFDPLTKQWTQAG | 134        |
| MOCKGYDILTKWCVTNG  | 135        |
| LWSKEVWDILTKSWVSOA | 136        |
| KAAGWWFDWLTKVWVPAP | 137        |
| AYQTFWDSLTRLWLSTT  | 138        |
| SGQHFWDLLTRSWTPST  | 139        |
| LGVGQKWDPLTKQWVSRG | 140        |
| VGKMCQWDPLIKRTVCVG | 141        |
| CRQGAFFDLLTKQCLLGR | 142        |
| GQAIRHWDVLTQWVDSQ  | 143        |
| RGPCGSWDLTKHCLDSQ  | 144        |
| WQWKQWDLTKQMVWVG   | 145        |
| PITICRKDLLTKQVVCLD | 146        |
| KTCNGKWDLLTKQCLQQA | 147        |
| KCLKGKWDLLTKQCVTEV | 148        |
| RCWNGKWDLLTKQCIHPW | 149        |
| NRDMRKWDPLIKQWIVRP | 150        |
| QAAAATWDLTKQWLVPV  | 151        |
| PEGGPKWDPLTKQFLPPV | 152        |
| QTPQKKWDLTKQWFTRN  | 153        |
| IGSPCKWDLTKQMICQT  | 154        |
| CTAAGKWDLLTKQCIQEK | 155        |
| VSQCMKWDLLTKQCLQGW | 156        |
| VWGTWKWDLTKQYLPPQ  | 157        |
| GWWEMKWDLLTKQWYRPQ | 158        |
| TAQVSKWDLTKQWLPLA  | 159        |
| QLWGTWDLTKQYIQIM   | 160        |
| WATSQKWDLLTKQWVQNM | 161        |
| QRQCAKWDLLTKQCVLFY | 162        |

|                     |     |
|---------------------|-----|
| KTTDCKWDLLTKQRICQV  | 163 |
| LLCQGWKDLLTKQCLKLR  | 164 |
| LMWFWKWDLLTKQLVPTF  | 165 |
| QWAWKWDLLTKQWIGPM   | 166 |
| NKELLKWDLLTKQCRGRS  | 167 |
| GQKDLKWDLLTKQYVRQS  | 168 |
| PKPCQKWDLLTKQCLGSV  | 169 |
| GQIGWKWDLLTKQWIQTR  | 170 |
| VWLDWKWDLLTKQWIHPQ  | 171 |
| QEWYKWDLLTKQGWGLR   | 172 |
| HWDSWKWDLLTKQWVVOA  | 173 |
| TRPLQKWDLLTKQWLRVG  | 174 |
| SDQWQKWDLLTKQWFWDV  | 175 |
| QQTFMKWDLLTKQWIRRH  | 176 |
| QGECKRWDLLTKQCFPGQ  | 177 |
| GQMGWRWDPLIKMCLGPS  | 178 |
| QLDGCKWDLLTKQKVCIP  | 179 |
| HGYWQKWDLLTKQWVSSE  | 180 |
| HQGGCGWDLLTRIYLPCH  | 181 |
| LHKACKWDLLTKQCWPMQ  | 182 |
| GPPGSVWDLLTKIWIQTG  | 183 |
| ITQDWRFDTLTRLWLPLR  | 184 |
| QGGFAAWDVLTKMWITVP  | 185 |
| GHGTPWWDALTRIWIIGV  | 186 |
| VWVPWQKWDLLTKQFVFQD | 187 |
| WQWSWKWDLLTRQYISSS  | 188 |
| NQTLWKWDLLTKQFITYM  | 60  |
| PVYQGWWDTLTKLYIWDG  | 61  |
| WLDGGWRDPLIKRSVQLG  | 62  |
| GHQQFKWDLLTKQWVQSN  | 63  |
| QRVGQFWDVLTKMFITGS  | 64  |
| QAQGWSYDALIKTWIRWP  | 65  |
| GWMHWKWDPLTKQALPWM  | 66  |
| GHPTYKWDLLTKQWILQM  | 67  |
| WNNWSLWDPLTKLWLQQN  | 68  |
| WQGWKWDLLTKQWVQQQ   | 69  |
| GQMGWRWDPLTKMWLGTS  | 70  |

It is noted that the known receptors for TALL-1 bear some sequence homology with preferred peptides:

12-3 LPGCKWDLLIKQWCDPL  
5 **BAFFR** MRRGPRSLRGRDAPVPTPCVPTECYDDLVRKCVDCRLL  
**TACI** TICNHQSQRTCAAFCSRSLSCRKEQGKFYDHLLRDCISCASI  
**BCMA** FVSPSQEIRGRFRRLQMAQCQSQNEYFDSLLHACIPCQLRC  
(SEQ ID NOS: 33, 195, 196, and 197, respectively).

Any peptide containing a cysteinyl residue may be cross-linked with  
10 another Cys-containing peptide, either or both of which may be linked to a



vehicle. Any peptide having more than one Cys residue may form an intrapeptide disulfide bond, as well. Any of these peptides may be derivatized as described hereinafter.

Additional useful peptide sequences may result from conservative  
5 and/or non-conservative modifications of the amino acid sequences of the sequences in Table 2.

Conservative modifications will produce peptides having functional and chemical characteristics similar to those of the peptide from which such modifications are made. In contrast, substantial modifications  
10 in the functional and/or chemical characteristics of the peptides may be accomplished by selecting substitutions in the amino acid sequence that differ significantly in their effect on maintaining (a) the structure of the molecular backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule  
15 at the target site, or (c) the size of the molecule.

For example, a "conservative amino acid substitution" may involve a substitution of a native amino acid residue with a nonnative residue such that there is little or no effect on the polarity or charge of the amino acid residue at that position. Furthermore, any native residue in the  
20 polypeptide may also be substituted with alanine, as has been previously described for "alanine scanning mutagenesis" (see, for example, MacLennan et al., 1998, Acta Physiol. Scand. Suppl. 643:55-67; Sasaki et al., 1998, Adv. Biophys. 35:1-24, which discuss alanine scanning mutagenesis).

Desired amino acid substitutions (whether conservative or non-  
25 conservative) can be determined by those skilled in the art at the time such substitutions are desired. For example, amino acid substitutions can be used to identify important residues of the peptide sequence, or to increase or decrease the affinity of the peptide or vehicle-peptide molecules (see preceding formulae) described herein. Exemplary amino acid  
30 substitutions are set forth in Table 3.

**Table 3—Amino Acid Substitutions**

| Original Residues | Exemplary Substitutions                 | Preferred Substitutions |
|-------------------|---|-------------------------|
| Ala (A)           | Val, Leu, Ile                           | Val                     |
| Arg (R)           | Lys, Gln, Asn                           | Lys                     |
| Asn (N)           | Gln                                     | Gln                     |
| Asp (D)           | Glu                                     | Glu                     |
| Cys (C)           | Ser, Ala                                | Ser                     |
| Gln (Q)           | Asn                                     | Asn                     |
| Glu (E)           | Asp                                     | Asp                     |
| Gly (G)           | Pro, Ala                                | Ala                     |
| His (H)           | Asn, Gln, Lys, Arg                      | Arg                     |
| Ile (I)           | Leu, Val, Met, Ala, Phe, Norleucine     | Leu                     |
| Leu (L)           | Norleucine, Ile, Val, Met, Ala, Phe     | Ile                     |
| Lys (K)           | Arg, 1,4 Diamino-butyric Acid, Gln, Asn | Arg                     |
| Met (M)           | Leu, Phe, Ile                           | Leu                     |
| Phe (F)           | Leu, Val, Ile, Ala, Tyr                 | Leu                     |
| Pro (P)           | Ala                                     | Gly                     |
| Ser (S)           | Thr, Ala, Cys                           | Thr                     |
| Thr (T)           | Ser                                     | Ser                     |
| Trp (W)           | Tyr, Phe                                | Tyr                     |
| Tyr (Y)           | Trp, Phe, Thr, Ser                      | Phe                     |
| Val (V)           | Ile, Met, Leu, Phe, Ala, Norleucine     | Leu                     |

5           In certain embodiments, conservative amino acid substitutions also encompass non-naturally occurring amino acid residues which are

typically incorporated by chemical peptide synthesis rather than by synthesis in biological systems.

As noted in the foregoing section "Definition of Terms," naturally occurring residues may be divided into classes based on common  
5 sidechain properties that may be useful for modifications of sequence. For example, non-conservative substitutions may involve the exchange of a member of one of these classes for a member from another class. Such substituted residues may be introduced into regions of the peptide that are homologous with non-human orthologs, or into the non-homologous  
10 regions of the molecule. In addition, one may also make modifications using P or G for the purpose of influencing chain orientation.

In making such modifications, the hydropathic index of amino acids may be considered. Each amino acid has been assigned a  
hydropathic index on the basis of their hydrophobicity and charge  
15 characteristics, these are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (-0.4); threonine (-0.7); serine (-0.8); tryptophan (-0.9); tyrosine (-1.3); proline (-1.6); histidine (-3.2); glutamate (-3.5); glutamine (-3.5); aspartate (-3.5); asparagine (-3.5); lysine (-3.9); and arginine (-4.5).

20 The importance of the hydropathic amino acid index in conferring interactive biological function on a protein is understood in the art. Kyte et al., *J. Mol. Biol.*, 157: 105-131 (1982). It is known that certain amino acids may be substituted for other amino acids having a similar hydropathic index or score and still retain a similar biological activity. In making  
25 changes based upon the hydropathic index, the substitution of amino acids whose hydropathic indices are within  $\pm 2$  is preferred, those which are within  $\pm 1$  are particularly preferred, and those within  $\pm 0.5$  are even more particularly preferred.

It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity. The greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with its immunogenicity and antigenicity, i.e., with a biological property of the protein.

The following hydrophilicity values have been assigned to amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0  $\pm$  1); glutamate (+3.0  $\pm$  1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (-0.4); proline (-0.5  $\pm$  1); alanine (-0.5); histidine (-0.5); cysteine (-1.0); methionine (-1.3); valine (-1.5); leucine (-1.8); isoleucine (-1.8); tyrosine (-2.3); phenylalanine (-2.5); tryptophan (-3.4). In making changes based upon similar hydrophilicity values, the substitution of amino acids whose hydrophilicity values are within  $\pm 2$  is preferred, those which are within  $\pm 1$  are particularly preferred, and those within  $\pm 0.5$  are even more particularly preferred. One may also identify epitopes from primary amino acid sequences on the basis of hydrophilicity. These regions are also referred to as "epitopic core regions."

A skilled artisan will be able to determine suitable variants of the polypeptide as set forth in the foregoing sequences using well known techniques. For identifying suitable areas of the molecule that may be changed without destroying activity, one skilled in the art may target areas not believed to be important for activity. For example, when similar polypeptides with similar activities from the same species or from other species are known, one skilled in the art may compare the amino acid sequence of a peptide to similar peptides. With such a comparison, one can identify residues and portions of the molecules that are conserved among similar polypeptides. It will be appreciated that changes in areas of a peptide that are not conserved relative to such similar peptides would

be less likely to adversely affect the biological activity and/or structure of the peptide. One skilled in the art would also know that, even in relatively conserved regions, one may substitute chemically similar amino acids for the naturally occurring residues while retaining activity (conservative amino acid residue substitutions). Therefore, even areas that may be important for biological activity or for structure may be subject to conservative amino acid substitutions without destroying the biological activity or without adversely affecting the peptide structure.

Additionally, one skilled in the art can review structure-function studies identifying residues in similar peptides that are important for activity or structure. In view of such a comparison, one can predict the importance of amino acid residues in a peptide that correspond to amino acid residues that are important for activity or structure in similar peptides. One skilled in the art may opt for chemically similar amino acid substitutions for such predicted important amino acid residues of the peptides.

One skilled in the art can also analyze the three-dimensional structure and amino acid sequence in relation to that structure in similar polypeptides. In view of that information, one skilled in the art may predict the alignment of amino acid residues of a peptide with respect to its three dimensional structure. One skilled in the art may choose not to make radical changes to amino acid residues predicted to be on the surface of the protein, since such residues may be involved in important interactions with other molecules. Moreover, one skilled in the art may generate test variants containing a single amino acid substitution at each desired amino acid residue. The variants can then be screened using activity assays known to those skilled in the art. Such data could be used to gather information about suitable variants. For example, if one discovered that a change to a particular amino acid residue resulted in destroyed,

undesirably reduced, or unsuitable activity, variants with such a change would be avoided. In other words, based on information gathered from such routine experiments, one skilled in the art can readily determine the amino acids where further substitutions should be avoided either alone or  
5 in combination with other mutations.

A number of scientific publications have been devoted to the prediction of secondary structure. See Moulton J., Curr. Op. in Biotech., 7(4): 422-427 (1996), Chou et al., Biochemistry, 13(2): 222-245 (1974); Chou et al., Biochemistry, 113(2): 211-222 (1974); Chou et al., Adv. Enzymol. Relat.  
10 Areas Mol. Biol., 47: 45-148 (1978); Chou et al., Ann. Rev. Biochem., 47: 251-276 and Chou et al., Biophys. J., 26: 367-384 (1979). Moreover, computer programs are currently available to assist with predicting secondary structure. One method of predicting secondary structure is based upon homology modeling. For example, two polypeptides or  
15 proteins which have a sequence identity of greater than 30%, or similarity greater than 40% often have similar structural topologies. The recent growth of the protein structural data base (PDB) has provided enhanced predictability of secondary structure, including the potential number of folds within a polypeptide's or protein's structure. See Holm et al., Nucl.  
20 Acid. Res., 27(1): 244-247 (1999). It has been suggested (Brenner et al., Curr. Op. Struct. Biol., 7(3): 369-376 (1997)) that there are a limited number of folds in a given polypeptide or protein and that once a critical number of structures have been resolved, structural prediction will gain dramatically in accuracy.

25 Additional methods of predicting secondary structure include "threading" (Jones, D., Curr. Opin. Struct. Biol., 7(3): 377-87 (1997); Sippl et al., Structure, 4(1): 15-9 (1996)), "profile analysis" (Bowie et al., Science, 253: 164-170 (1991); Gribskov et al., Meth. Enzym., 183: 146-159 (1990);

Gribskov *et al.*, *Proc. Nat. Acad. Sci.*, 84(13): 4355-8 (1987)), and “evolutionary linkage” (See Home, *supra*, and Brenner, *supra*).

Vehicles. This invention requires the presence of at least one vehicle (V<sup>1</sup>) attached to a peptide through the N-terminus, C-terminus or a sidechain of one of the amino acid residues. Multiple vehicles may also be used; e.g., Fc’s at each terminus or an Fc at a terminus and a PEG group at the other terminus or a sidechain. Exemplary vehicles include:

- an Fc domain;
- other proteins, polypeptides, or peptides capable of binding to a salvage receptor;
- human serum albumin (HSA);
- a leucine zipper (LZ) domain;
- polyethylene glycol (PEG), including 5 kD, 20 kD, and 30 kD PEG, as well as other polymers;
- dextran;

and other molecules known in the art to provide extended half-life and/or protection from proteolytic degradation or clearance.

An Fc domain is the preferred vehicle. The Fc domain may be fused to the N or C termini of the peptides or at both the N and C termini.

Fusion to the N terminus is preferred.

As noted above, Fc variants are suitable vehicles within the scope of this invention. A native Fc may be extensively modified to form an Fc variant in accordance with this invention, provided binding to the salvage receptor is maintained; see, for example WO 97/34631 and WO 96/32478.

In such Fc variants, one may remove one or more sites of a native Fc that provide structural features or functional activity not required by the fusion molecules of this invention. One may remove these sites by, for example, substituting or deleting residues, inserting residues into the site, or truncating portions containing the site. The inserted or substituted

residues may also be altered amino acids, such as peptidomimetics or D-amino acids. Fc variants may be desirable for a number of reasons, several of which are described below. Exemplary Fc variants include molecules and sequences in which:

- 5 1. Sites involved in disulfide bond formation are removed. Such removal may avoid reaction with other cysteine-containing proteins present in the host cell used to produce the molecules of the invention. For this purpose, the cysteine-containing segment at the N-terminus may be truncated or cysteine residues may be deleted or substituted with other  
10 amino acids (e.g., alanyl, seryl). In particular, one may truncate the N-terminal 20-amino acid segment of SEQ ID NO: 2 or delete or substitute the cysteine residues at positions 7 and 10 of SEQ ID NO: 2. Even when cysteine residues are removed, the single chain Fc domains can still form a dimeric Fc domain that is held together non-covalently.
- 15 2. A native Fc is modified to make it more compatible with a selected host cell. For example, one may remove the PA sequence near the N-terminus of a typical native Fc, which may be recognized by a digestive enzyme in E. coli such as proline iminopeptidase. One may also add an N-terminal methionine residue, especially when the molecule is  
20 expressed recombinantly in a bacterial cell such as E. coli. The Fc domain of SEQ ID NO: 2 is one such Fc variant.
3. A portion of the N-terminus of a native Fc is removed to prevent N-terminal heterogeneity when expressed in a selected host cell. For this purpose, one may delete any of the first 20 amino acid residues at the  
25 N-terminus, particularly those at positions 1, 2, 3, 4 and 5.
4. One or more glycosylation sites are removed. Residues that are typically glycosylated (e.g., asparagine) may confer cytolytic response. Such residues may be deleted or substituted with unglycosylated residues (e.g., alanine).



- 5 5. Sites involved in interaction with complement, such as the C1q binding site, are removed. For example, one may delete or substitute the EKK sequence of human IgG1. Complement recruitment may not be advantageous for the molecules of this invention and so may be avoided with such an Fc variant.
6. Sites are removed that affect binding to Fc receptors other than a salvage receptor. A native Fc may have sites for interaction with certain white blood cells that are not required for the fusion molecules of the present invention and so may be removed.
- 10 7. The ADCC site is removed. ADCC sites are known in the art; see, for example, Molec. Immunol. 29 (5): 633-9 (1992) with regard to ADCC sites in IgG1. These sites, as well, are not required for the fusion molecules of the present invention and so may be removed.
- 15 8. When the native Fc is derived from a non-human antibody, the native Fc may be humanized. Typically, to humanize a native Fc, one will substitute selected residues in the non-human native Fc with residues that are normally found in human native Fc. Techniques for antibody humanization are well known in the art.

Preferred Fc variants include the following. In SEQ ID NO: 2  
20 (Figure 3), the leucine at position 15 may be substituted with glutamate; the glutamate at position 99, with alanine; and the lysines at positions 101 and 103, with alanines. In addition, one or more tyrosine residues can be replaced by phenylalanine residues.

25 An alternative vehicle would be a protein, polypeptide, peptide, antibody, antibody fragment, or small molecule (e.g., a peptidomimetic compound) capable of binding to a salvage receptor. For example, one could use as a vehicle a polypeptide as described in U.S. Pat. No. 5,739,277, issued April 14, 1998 to Presta et al. Peptides could also be selected by phage display or RNA-peptide screening for binding to the

FcRn salvage receptor. Such salvage receptor-binding compounds are also included within the meaning of "vehicle" and are within the scope of this invention. Such vehicles should be selected for increased half-life (e.g., by avoiding sequences recognized by proteases) and decreased  
5 immunogenicity (e.g., by favoring non-immunogenic sequences, as discovered in antibody humanization).

As noted above, polymer vehicles may also be used for V<sup>1</sup>. Various means for attaching chemical moieties useful as vehicles are currently available, see, e.g., Patent Cooperation Treaty ("PCT") International  
10 Publication No. WO 96/11953, entitled "N-Terminally Chemically Modified Protein Compositions and Methods," herein incorporated by reference in its entirety. This PCT publication discloses, among other things, the selective attachment of water soluble polymers to the N-terminus of proteins.

15 A preferred polymer vehicle is polyethylene glycol (PEG). The PEG group may be of any convenient molecular weight and may be linear or branched. The average molecular weight of the PEG will preferably range from about 2 kiloDalton ("kD") to about 100 kD, more preferably from about 5 kD to about 50 kD, most preferably from about 5 kD to about 10  
20 kD. The PEG groups will generally be attached to the compounds of the invention via acylation or reductive alkylation through a reactive group on the PEG moiety (e.g., an aldehyde, amino, thiol, or ester group) to a reactive group on the inventive compound (e.g., an aldehyde, amino, or ester group).

25 A useful strategy for the PEGylation of synthetic peptides consists of combining, through forming a conjugate linkage in solution, a peptide and a PEG moiety, each bearing a special functionality that is mutually reactive toward the other. The peptides can be easily prepared with conventional solid phase synthesis. The peptides are "preactivated" with

an appropriate functional group at a specific site. The precursors are purified and fully characterized prior to reacting with the PEG moiety. Ligation of the peptide with PEG usually takes place in aqueous phase and can be easily monitored by reverse phase analytical HPLC. The PEGylated peptides can be easily purified by preparative HPLC and characterized by analytical HPLC, amino acid analysis and laser desorption mass spectrometry.

Polysaccharide polymers are another type of water soluble polymer which may be used for protein modification. Dextrans are polysaccharide polymers comprised of individual subunits of glucose predominantly linked by  $\alpha$ 1-6 linkages. The dextran itself is available in many molecular weight ranges, and is readily available in molecular weights from about 1 kD to about 70 kD. Dextran is a suitable water soluble polymer for use in the present invention as a vehicle by itself or in combination with another vehicle (e.g., Fc). See, for example, WO 96/11953 and WO 96/05309. The use of dextran conjugated to therapeutic or diagnostic immunoglobulins has been reported; see, for example, European Patent Publication No. 0 315 456, which is hereby incorporated by reference in its entirety. Dextran of about 1 kD to about 20 kD is preferred when dextran is used as a vehicle in accordance with the present invention.

Linkers. Any "linker" group is optional. When present, its chemical structure is not critical, since it serves primarily as a spacer. The linker is preferably made up of amino acids linked together by peptide bonds. Thus, in preferred embodiments, the linker is made up of from 1 to 30 amino acids linked by peptide bonds, wherein the amino acids are selected from the 20 naturally occurring amino acids. Some of these amino acids may be glycosylated, as is well understood by those in the art. In a more preferred embodiment, the 1 to 20 amino acids are selected from glycine, alanine, proline, asparagine, glutamine, and lysine. Even more preferably,

a linker is made up of a majority of amino acids that are sterically unhindered, such as glycine and alanine. Thus, preferred linkers are polyglycines (particularly (Gly)<sub>4</sub>, (Gly)<sub>5</sub>), poly(Gly-Ala), and polyalanines. Other specific examples of linkers are:

- 5 (Gly)<sub>3</sub>Lys(Gly)<sub>4</sub> (SEQ ID NO: 40);  
 (Gly)<sub>3</sub>AsnGlySer(Gly)<sub>2</sub> (SEQ ID NO: 41);  
 (Gly)<sub>3</sub>Cys(Gly)<sub>4</sub> (SEQ ID NO: 42); and  
 GlyProAsnGlyGly (SEQ ID NO: 43).

To explain the above nomenclature, for example, (Gly)<sub>3</sub>Lys(Gly)<sub>4</sub> means  
 10 Gly-Gly-Gly-Lys-Gly-Gly-Gly-Gly (SEQ ID NO: 40). Combinations of Gly and Ala are also preferred. The linkers shown here are exemplary; linkers within the scope of this invention may be much longer and may include other residues.

Preferred linkers are amino acid linkers comprising greater than 5  
 15 amino acids, with suitable linkers having up to about 500 amino acids selected from glycine, alanine, proline, asparagine, glutamine, lysine, threonine, serine or aspartate. Linkers of about 20 to 50 amino acids are most preferred. One group of preferred linkers are those of the formulae

20 GSGSATGGSGSTASSGSGSATx<sup>1</sup>x<sup>2</sup>  
 (SEQ ID NO: 193)

and

GSGSATGGSGSTASSGSGSATx<sup>1</sup>x<sup>2</sup>GSGSATGGSGSTASSGSGSATx<sup>3</sup>x<sup>4</sup>  
 (SEQ ID NO: 194)

wherein x<sup>1</sup> and x<sup>3</sup> are each independently basic or hydrophobic residues  
 25 and x<sup>2</sup> and x<sup>4</sup> are each independently hydrophobic residues. Specific preferred linkers are:

GSGSATGGSGSTASSGSGSATHM  
 (SEQ ID NO: 59)

GSGSATGGSGSTASSGSGSATGM

(SEQ ID NO: 190)

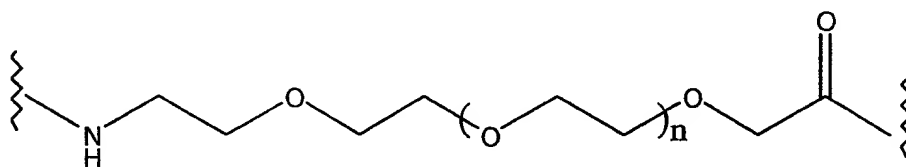
GSGSATGGSGSTASSGSGSATGS

(SEQ ID NO: 191), and

5 GSGSATGGSGSTASSGSGSATHMGSGSATGGSGSTASSGSGSATHM  
(SEQ ID NO: 192).

Non-peptide linkers are also possible. For example, alkyl linkers such as  $\text{-NH-(CH}_2\text{)}_s\text{-C(O)-}$ , wherein  $s = 2\text{-}20$  could be used. These alkyl linkers may further be substituted by any non-sterically hindering group  
10 such as lower alkyl (e.g.,  $\text{C}_1\text{-C}_6$ ) lower acyl, halogen (e.g., Cl, Br), CN,  $\text{NH}_2$ , phenyl, etc. An exemplary non-peptide linker is a PEG linker,

VII



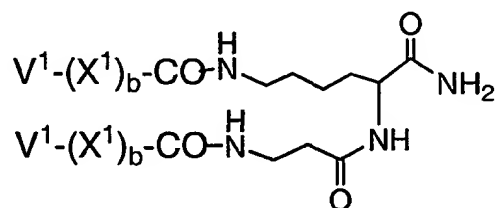
15 wherein  $n$  is such that the linker has a molecular weight of 100 to 5000 kD, preferably 100 to 500 kD. The peptide linkers may be altered to form derivatives in the same manner as described above.

Derivatives. The inventors also contemplate derivatizing the peptide and/or vehicle portion of the compounds. Such derivatives may  
20 improve the solubility, absorption, biological half life, and the like of the compounds. The moieties may alternatively eliminate or attenuate any undesirable side-effect of the compounds and the like. Exemplary derivatives include compounds in which:

1. The compound or some portion thereof is cyclic. For example, the  
25 peptide portion may be modified to contain two or more Cys residues (e.g., in the linker), which could cyclize by disulfide bond formation.

2. The compound is cross-linked or is rendered capable of cross-linking between molecules. For example, the peptide portion may be modified to contain one Cys residue and thereby be able to form an intermolecular disulfide bond with a like molecule. The compound  
5 may also be cross-linked through its C-terminus, as in the molecule shown below.

## VIII



10 In Formula VIII, each "V<sup>1</sup>" may represent typically one strand of the Fc domain.

3. One or more peptidyl [-C(O)NR-] linkages (bonds) is replaced by a non-peptidyl linkage. Exemplary non-peptidyl linkages are -CH<sub>2</sub>-carbamate [-CH<sub>2</sub>-OC(O)NR-], phosphonate, -CH<sub>2</sub>-sulfonamide [-CH<sub>2</sub>-S(O)<sub>2</sub>NR-], urea [-NHC(O)NH-], -CH<sub>2</sub>-secondary amine, and alkylated peptide [-C(O)NR<sup>6</sup>- wherein R<sup>6</sup> is lower alkyl].
- 15 4. The N-terminus is derivatized. Typically, the N-terminus may be acylated or modified to a substituted amine. Exemplary N-terminal derivative groups include -NRR<sup>1</sup> (other than -NH<sub>2</sub>), -NRC(O)R<sup>1</sup>, -NRC(O)OR<sup>1</sup>, -NRS(O)<sub>2</sub>R<sup>1</sup>, -NHC(O)NHR<sup>1</sup>, succinimide, or  
20 benzyloxycarbonyl-NH- (CBZ-NH-), wherein R and R<sup>1</sup> are each independently hydrogen or lower alkyl and wherein the phenyl ring may be substituted with 1 to 3 substituents selected from the group consisting of C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, chloro, and bromo.
5. The free C-terminus is derivatized. Typically, the C-terminus is  
25 esterified or amidated. Exemplary C-terminal derivative groups include, for example, -C(O)R<sup>2</sup> wherein R<sup>2</sup> is lower alkoxy or -NR<sup>3</sup>R<sup>4</sup>

wherein R<sup>3</sup> and R<sup>4</sup> are independently hydrogen or C<sub>1</sub>-C<sub>8</sub> alkyl (preferably C<sub>1</sub>-C<sub>4</sub> alkyl).

6. A disulfide bond is replaced with another, preferably more stable, cross-linking moiety (e.g., an alkylene). See, e.g., Bhatnagar *et al.* (1996), *J. Med. Chem.* 39: 3814-9; Alberts *et al.* (1993) *Thirteenth Am. Pep. Symp.*, 357-9.
7. One or more individual amino acid residues is modified. Various derivatizing agents are known to react specifically with selected sidechains or terminal residues, as described in detail below.

10        Lysinyl residues and amino terminal residues may be reacted with succinic or other carboxylic acid anhydrides, which reverse the charge of the lysinyl residues. Other suitable reagents for derivatizing alpha-amino-containing residues include imidoesters such as methyl picolinimide; pyridoxal phosphate; pyridoxal; chloroborohydride; trinitrobenzenesulfonic  
15    acid; O-methylisourea; 2,4 pentanedione; and transaminase-catalyzed reaction with glyoxylate.

      Arginyl residues may be modified by reaction with any one or combination of several conventional reagents, including phenylglyoxal, 2,3-butanedione, 1,2-cyclohexanedione, and ninhydrin. Derivatization of arginyl  
20    residues requires that the reaction be performed in alkaline conditions because of the high pKa of the guanidine functional group. Furthermore, these reagents may react with the groups of lysine as well as the arginine epsilon-amino group.

      Specific modification of tyrosyl residues has been studied extensively,  
25    with particular interest in introducing spectral labels into tyrosyl residues by reaction with aromatic diazonium compounds or tetranitromethane. Most commonly, N-acetylimidazole and tetranitromethane are used to form O-acetyl tyrosyl species and 3-nitro derivatives, respectively.

Carboxyl sidechain groups (aspartyl or glutamyl) may be selectively modified by reaction with carbodiimides ( $R'-N=C=N-R'$ ) such as 1-cyclohexyl-3-(2-morpholinyl-(4-ethyl) carbodiimide or 1-ethyl-3-(4-azonia-4,4-dimethylpentyl) carbodiimide. Furthermore, aspartyl and glutamyl residues  
5 may be converted to asparaginyll and glutaminyll residues by reaction with ammonium ions.

Glutaminyll and asparaginyll residues may be deamidated to the corresponding glutamyl and aspartyl residues. Alternatively, these residues are deamidated under mildly acidic conditions. Either form of these residues  
10 falls within the scope of this invention.

Cysteinyl residues can be replaced by amino acid residues or other moieties either to eliminate disulfide bonding or, conversely, to stabilize cross-linking. See, e.g., Bhatnagar *et al.* (1996), *J. Med. Chem.* 39: 3814-9.

Derivatization with bifunctional agents is useful for cross-linking the  
15 peptides or their functional derivatives to a water-insoluble support matrix or to other macromolecular vehicles. Commonly used cross-linking agents include, e.g., 1,1-bis(diazoacetyl)-2-phenylethane, glutaraldehyde, N-hydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'-  
20 dithiobis(succinimidylpropionate), and bifunctional maleimides such as bis-N-maleimido-1,8-octane. Derivatizing agents such as methyl-3-[(p-azidophenyl)dithio]propioimide yield photoactivatable intermediates that are capable of forming cross-links in the presence of light. Alternatively, reactive water-insoluble matrices such as cyanogen bromide-activated carbohydrates  
25 and the reactive substrates described in U.S. Pat. Nos. 3,969,287; 3,691,016; 4,195,128; 4,247,642; 4,229,537; and 4,330,440 are employed for protein immobilization.

Carbohydrate (oligosaccharide) groups may conveniently be attached to sites that are known to be glycosylation sites in proteins.



Generally, O-linked oligosaccharides are attached to serine (Ser) or threonine (Thr) residues while N-linked oligosaccharides are attached to asparagine (Asn) residues when they are part of the sequence Asn-X-Ser/Thr, where X can be any amino acid except proline. X is preferably one of the 19 naturally occurring amino acids other than proline. The structures of N-linked and O-linked oligosaccharides and the sugar residues found in each type are different. One type of sugar that is commonly found on both is N-acetylneuraminic acid (referred to as sialic acid). Sialic acid is usually the terminal residue of both N-linked and O-linked oligosaccharides and, by virtue of its negative charge, may confer acidic properties to the glycosylated compound. Such site(s) may be incorporated in the linker of the compounds of this invention and are preferably glycosylated by a cell during recombinant production of the polypeptide compounds (e.g., in mammalian cells such as CHO, BHK, COS). However, such sites may further be glycosylated by synthetic or semi-synthetic procedures known in the art.

Other possible modifications include hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, oxidation of the sulfur atom in Cys, methylation of the alpha-amino groups of lysine, arginine, and histidine side chains. Creighton, Proteins: Structure and Molecule Properties (W. H. Freeman & Co., San Francisco), pp. 79-86 (1983).

Compounds of the present invention may be changed at the DNA level, as well. The DNA sequence of any portion of the compound may be changed to codons more compatible with the chosen host cell. For E. coli, which is the preferred host cell, optimized codons are known in the art. Codons may be substituted to eliminate restriction sites or to include silent restriction sites, which may aid in processing of the DNA in the selected

host cell. The vehicle, linker and peptide DNA sequences may be modified to include any of the foregoing sequence changes.

### **Methods of Making**

The compounds of this invention largely may be made in  
5 transformed host cells using recombinant DNA techniques. To do so, a recombinant DNA molecule coding for the peptide is prepared. Methods of preparing such DNA molecules are well known in the art. For instance, sequences coding for the peptides could be excised from DNA using suitable restriction enzymes. Alternatively, the DNA molecule could be  
10 synthesized using chemical synthesis techniques, such as the phosphoramidate method. Also, a combination of these techniques could be used.

The invention also includes a vector capable of expressing the peptides in an appropriate host. The vector comprises the DNA molecule  
15 that codes for the peptides operatively linked to appropriate expression control sequences. Methods of effecting this operative linking, either before or after the DNA molecule is inserted into the vector, are well known. Expression control sequences include promoters, activators, enhancers, operators, ribosomal binding sites, start signals, stop signals,  
20 cap signals, polyadenylation signals, and other signals involved with the control of transcription or translation.

The resulting vector having the DNA molecule thereon is used to transform an appropriate host. This transformation may be performed using methods well known in the art.

25 Any of a large number of available and well-known host cells may be used in the practice of this invention. The selection of a particular host is dependent upon a number of factors recognized by the art. These include, for example, compatibility with the chosen expression vector, toxicity of the peptides encoded by the DNA molecule, rate of

transformation, ease of recovery of the peptides, expression characteristics, bio-safety and costs. A balance of these factors must be struck with the understanding that not all hosts may be equally effective for the expression of a particular DNA sequence. Within these general guidelines, 5 useful microbial hosts include bacteria (such as E. coli sp.), yeast (such as Saccharomyces sp.) and other fungi, insects, plants, mammalian (including human) cells in culture, or other hosts known in the art.

Next, the transformed host is cultured and purified. Host cells may be cultured under conventional fermentation conditions so that the 10 desired compounds are expressed. Such fermentation conditions are well known in the art. Finally, the peptides are purified from culture by methods well known in the art.

The compounds may also be made by synthetic methods. For example, solid phase synthesis techniques may be used. Suitable 15 techniques are well known in the art, and include those described in Merrifield (1973), Chem. Polypeptides, pp. 335-61 (Katsoyannis and Panayotis eds.); Merrifield (1963), J. Am. Chem. Soc. 85: 2149; Davis et al. (1985), Biochem. Intl. 10: 394-414; Stewart and Young (1969), Solid Phase Peptide Synthesis; U.S. Pat. No. 3,941,763; Finn et al. (1976), The Proteins 20 (3rd ed.) 2: 105-253; and Erickson et al. (1976), The Proteins (3rd ed.) 2: 257-527. Solid phase synthesis is the preferred technique of making individual peptides since it is the most cost-effective method of making small peptides.

Compounds that contain derivatized peptides or which contain 25 non-peptide groups may be synthesized by well-known organic chemistry techniques.

#### Uses of the Compounds

Compounds of this invention may be particularly useful in treatment of B-cell mediated autoimmune diseases. In particular, the

compounds of this invention may be useful in treating, preventing, ameliorating, diagnosing or prognosing lupus, including systemic lupus erythematosus (SLE), and lupus-associated diseases and conditions. Other preferred indications include B-cell mediated cancers, including B-cell  
5 lymphoma.

The compounds of this invention can also be used to treat inflammatory conditions of the joints. Inflammatory conditions of a joint are chronic joint diseases that afflict and disable, to varying degrees, millions of people worldwide. Rheumatoid arthritis is a disease of  
10 articular joints in which the cartilage and bone are slowly eroded away by a proliferative, invasive connective tissue called pannus, which is derived from the synovial membrane. The disease may involve peri-articular structures such as bursae, tendon sheaths and tendons as well as extra-articular tissues such as the subcutis, cardiovascular system, lungs, spleen,  
15 lymph nodes, skeletal muscles, nervous system (central and peripheral) and eyes (Silberberg (1985), Anderson's Pathology, Kissane (ed.), II:1828). Osteoarthritis is a common joint disease characterized by degenerative changes in articular cartilage and reactive proliferation of bone and cartilage around the joint. Osteoarthritis is a cell-mediated active process  
20 that may result from the inappropriate response of chondrocytes to catabolic and anabolic stimuli. Changes in some matrix molecules of articular cartilage reportedly occur in early osteoarthritis (Thonar et al. (1993), Rheumatic disease clinics of North America, Moskowitz (ed.), 19:635-657 and Shinmei et al. (1992), Arthritis Rheum., 35:1304-1308).  
25 TALL-1, TALL-1R and modulators thereof are believed to be useful in the treatment of these and related conditions.

Compounds of this invention may also be useful in treatment of a number of additional diseases and disorders, including:

- acute pancreatitis;

- ALS;
- Alzheimer's disease;
- asthma;
- atherosclerosis;
- 5   • autoimmune hemolytic anemia;
- cancer, particularly cancers related to B cells;
- cachexia/anorexia;
- chronic fatigue syndrome;
- cirrhosis (e.g., primary biliary cirrhosis);
- 10   • diabetes (e.g., insulin diabetes);
- fever;
- glomerulonephritis, including IgA glomerulonephritis and  
primary glomerulonephritis;
- Goodpasture's syndrome;
- 15   • Guillain-Barre syndrome;
- graft versus host disease;
- Hashimoto's thyroiditis;
- hemorrhagic shock;
- hyperalgesia;
- 20   • inflammatory bowel disease;
- inflammatory conditions of a joint, including osteoarthritis,  
psoriatic arthritis and rheumatoid arthritis;
- inflammatory conditions resulting from strain, sprain, cartilage  
damage, trauma, orthopedic surgery, infection or other disease  
25   processes;
- insulin-dependent diabetes mellitus;

- ischemic injury, including cerebral ischemia (e.g., brain injury as a result of trauma, epilepsy, hemorrhage or stroke, each of which may lead to neurodegeneration);
- learning impairment;
- 5      • lung diseases (e.g., ARDS);
- multiple myeloma;
- multiple sclerosis;
- Myasthenia gravis;
- myelogenous (e.g., AML and CML) and other leukemias;
- 10    • myopathies (e.g., muscle protein metabolism, esp. in sepsis);
- neurotoxicity (e.g., as induced by HIV);
- osteoporosis;
- pain;
- Parkinson's disease;
- 15    • Pemphigus;
- polymyositis/dermatomyositis;
- pulmonary inflammation, including autoimmune pulmonary inflammation;
- pre-term labor;
- 20    • psoriasis;
- Reiter's disease;
- reperfusion injury;
- septic shock;
- side effects from radiation therapy;
- 25    • Sjogren's syndrome;
- sleep disturbance;
- temporal mandibular joint disease;

- thrombocytopenia, including idiopathic thrombocytopenia and autoimmune neonatal thrombocytopenia;
- tumor metastasis;
- uveitis; and
- vasculitis.

5

Compounds of this invention may be administered alone or in combination with a therapeutically effective amount of other drugs, including analgesic agents, disease-modifying anti-rheumatic drugs (DMARDs), non-steroidal anti-inflammatory drugs (NSAIDs), and any  
10 immune and/or inflammatory modulators. Thus, compounds of this invention may be administered with:

- Modulators of other members of the TNF/TNF receptor family, including TNF antagonists, such as etanercept (Enbrel™), sTNF-RI, onercept, D2E7, and Remicade™.
- 15 • Nerve growth factor (NGF) modulators.
- IL-1 inhibitors, including IL-1ra molecules such as anakinra and more recently discovered IL-1ra-like molecules such as IL-1Hy1 and IL-1Hy2; IL-1 "trap" molecules as described in U.S. Pat. No. 5,844,099, issued December 1, 1998; IL-1 antibodies; solubilized  
20 IL-1 receptor, and the like.
- IL-6 inhibitors (e.g., antibodies to IL-6).
- IL-8 inhibitors (e.g., antibodies to IL-8).
- IL-18 inhibitors (e.g., IL-18 binding protein, solubilized IL-18 receptor, or IL-18 antibodies).
- 25 • Interleukin-1 converting enzyme (ICE) modulators.
- insulin-like growth factors (IGF-1, IGF-2) and modulators thereof.
- Transforming growth factor- $\beta$  (TGF- $\beta$ ), TGF- $\beta$  family members, and TGF- $\beta$  modulators.

- Fibroblast growth factors FGF-1 to FGF-10, and FGF modulators.
- Osteoprotegerin (OPG), OPG analogues, osteoprotective agents, and antibodies to OPG-ligand (OPG-L).
- 5 • bone anabolic agents, such as parathyroid hormone (PTH), PTH fragments, and molecules incorporating PTH fragments (e.g., PTH (1-34)-Fc).
- PAF antagonists.
- Keratinocyte growth factor (KGF), KGF-related molecules (e.g.,  
10 KGF-2), and KGF modulators.
- COX-2 inhibitors, such as Celebrex™ and Vioxx™.
- Prostaglandin analogs (e.g., E series prostaglandins).
- Matrix metalloproteinase (MMP) modulators.
- Nitric oxide synthase (NOS) modulators, including modulators  
15 of inducible NOS.
- Modulators of glucocorticoid receptor.
- Modulators of glutamate receptor.
- Modulators of lipopolysaccharide (LPS) levels.
- Anti-cancer agents, including inhibitors of oncogenes (e.g., fos,  
20 jun) and interferons.
- Noradrenaline and modulators and mimetics thereof.



### Pharmaceutical Compositions

In General. The present invention also provides methods of using pharmaceutical compositions of the inventive compounds. Such pharmaceutical compositions may be for administration for injection, or for  
5 oral, pulmonary, nasal, transdermal or other forms of administration. In general, the invention encompasses pharmaceutical compositions comprising effective amounts of a compound of the invention together with pharmaceutically acceptable diluents, preservatives, solubilizers, emulsifiers, adjuvants and/or carriers. Such compositions include diluents of various  
10 buffer content (e.g., Tris-HCl, acetate, phosphate), pH and ionic strength; additives such as detergents and solubilizing agents (e.g., Tween 80, Polysorbate 80), anti-oxidants (e.g., ascorbic acid, sodium metabisulfite), preservatives (e.g., Thimersol, benzyl alcohol) and bulking substances (e.g., lactose, mannitol); incorporation of the material into particulate preparations of  
15 polymeric compounds such as polylactic acid, polyglycolic acid, etc. or into liposomes. Hyaluronic acid may also be used, and this may have the effect of promoting sustained duration in the circulation. Such compositions may influence the physical state, stability, rate of in vivo release, and rate of in vivo clearance of the present proteins and derivatives. See, e.g., Remington's  
20 Pharmaceutical Sciences, 18th Ed. (1990, Mack Publishing Co., Easton, PA 18042) pages 1435-1712 which are herein incorporated by reference in their entirety. The compositions may be prepared in liquid form, or may be in dried powder, such as lyophilized form. Implantable sustained release formulations are also contemplated, as are transdermal formulations.

25 Oral dosage forms. Contemplated for use herein are oral solid dosage forms, which are described generally in Chapter 89 of Remington's Pharmaceutical Sciences (1990), 18th Ed., Mack Publishing Co. Easton PA 18042, which is herein incorporated by reference in its entirety. Solid dosage forms include tablets, capsules, pills, troches or lozenges, cachets

or pellets. Also, liposomal or proteinoid encapsulation may be used to formulate the present compositions (as, for example, proteinoid microspheres reported in U.S. Patent No. 4,925,673). Liposomal encapsulation may be used and the liposomes may be derivatized with various polymers (e.g., U.S. Patent No. 5,013,556). A description of possible solid dosage forms for the therapeutic is given in Chapter 10 of Marshall, K., Modern Pharmaceutics (1979), edited by G. S. Banker and C. T. Rhodes, herein incorporated by reference in its entirety. In general, the formulation will include the inventive compound, and inert ingredients which allow for protection against the stomach environment, and release of the biologically active material in the intestine.

Also specifically contemplated are oral dosage forms of the above inventive compounds. If necessary, the compounds may be chemically modified so that oral delivery is efficacious. Generally, the chemical modification contemplated is the attachment of at least one moiety to the compound molecule itself, where said moiety permits (a) inhibition of proteolysis; and (b) uptake into the blood stream from the stomach or intestine. Also desired is the increase in overall stability of the compound and increase in circulation time in the body. Moieties useful as covalently attached vehicles in this invention may also be used for this purpose. Examples of such moieties include: PEG, copolymers of ethylene glycol and propylene glycol, carboxymethyl cellulose, dextran, polyvinyl alcohol, polyvinyl pyrrolidone and polyproline. See, for example, Abuchowski and Davis, Soluble Polymer-Enzyme Adducts, Enzymes as Drugs (1981), Hocenberg and Roberts, eds., Wiley-Interscience, New York, NY, , pp. 367-83; Newmark, et al. (1982), J. Appl. Biochem. 4:185-9. Other polymers that could be used are poly-1,3-dioxolane and poly-1,3,6-tioxocane. Preferred for pharmaceutical usage, as indicated above, are PEG moieties.

For oral delivery dosage forms, it is also possible to use a salt of a modified aliphatic amino acid, such as sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC), as a carrier to enhance absorption of the therapeutic compounds of this invention. The clinical efficacy of a heparin  
5 formulation using SNAC has been demonstrated in a Phase II trial conducted by Emisphere Technologies. See US Patent No. 5,792,451, "Oral drug delivery composition and methods".

The compounds of this invention can be included in the formulation as fine multiparticulates in the form of granules or pellets of  
10 particle size about 1 mm. The formulation of the material for capsule administration could also be as a powder, lightly compressed plugs or even as tablets. The therapeutic could be prepared by compression.

Colorants and flavoring agents may all be included. For example, the protein (or derivative) may be formulated (such as by liposome or  
15 microsphere encapsulation) and then further contained within an edible product, such as a refrigerated beverage containing colorants and flavoring agents.

One may dilute or increase the volume of the compound of the invention with an inert material. These diluents could include  
20 carbohydrates, especially mannitol,  $\alpha$ -lactose, anhydrous lactose, cellulose, sucrose, modified dextrans and starch. Certain inorganic salts may also be used as fillers including calcium triphosphate, magnesium carbonate and sodium chloride. Some commercially available diluents are Fast-Flo, Emdex, STA-Rx 1500, Emcompress and Avicell.

25 Disintegrants may be included in the formulation of the therapeutic into a solid dosage form. Materials used as disintegrants include but are not limited to starch including the commercial disintegrant based on starch, Explotab. Sodium starch glycolate, Amberlite, sodium carboxymethylcellulose, ultramylopectin, sodium alginate, gelatin, orange

peel, acid carboxymethyl cellulose, natural sponge and bentonite may all be used. Another form of the disintegrants are the insoluble cationic exchange resins. Powdered gums may be used as disintegrants and as binders and these can include powdered gums such as agar, Karaya or  
5 tragacanth. Alginic acid and its sodium salt are also useful as disintegrants.

Binders may be used to hold the therapeutic agent together to form a hard tablet and include materials from natural products such as acacia, tragacanth, starch and gelatin. Others include methyl cellulose (MC), ethyl  
10 cellulose (EC) and carboxymethyl cellulose (CMC). Polyvinyl pyrrolidone (PVP) and hydroxypropylmethyl cellulose (HPMC) could both be used in alcoholic solutions to granulate the therapeutic.

An antifrictional agent may be included in the formulation of the therapeutic to prevent sticking during the formulation process. Lubricants  
15 may be used as a layer between the therapeutic and the die wall, and these can include but are not limited to; stearic acid including its magnesium and calcium salts, polytetrafluoroethylene (PTFE), liquid paraffin, vegetable oils and waxes. Soluble lubricants may also be used such as sodium lauryl sulfate, magnesium lauryl sulfate, polyethylene glycol of  
20 various molecular weights, Carbowax 4000 and 6000.

Glidants that might improve the flow properties of the drug during formulation and to aid rearrangement during compression might be added. The glidants may include starch, talc, pyrogenic silica and hydrated silicoaluminate.

25 To aid dissolution of the compound of this invention into the aqueous environment a surfactant might be added as a wetting agent. Surfactants may include anionic detergents such as sodium lauryl sulfate, dioctyl sodium sulfosuccinate and dioctyl sodium sulfonate. Cationic detergents might be used and could include benzalkonium chloride or

benzethonium chloride. The list of potential nonionic detergents that could be included in the formulation as surfactants are lauromacrogol 400, polyoxyl 40 stearate, polyoxyethylene hydrogenated castor oil 10, 50 and 60, glycerol monostearate, polysorbate 40, 60, 65 and 80, sucrose fatty acid ester, methyl cellulose and carboxymethyl cellulose. These surfactants could be present in the formulation of the protein or derivative either alone or as a mixture in different ratios.

Additives may also be included in the formulation to enhance uptake of the compound. Additives potentially having this property are for instance the fatty acids oleic acid, linoleic acid and linolenic acid.

Controlled release formulation may be desirable. The compound of this invention could be incorporated into an inert matrix which permits release by either diffusion or leaching mechanisms; e.g., gums. Slowly degrading matrices may also be incorporated into the formulation, e.g., alginates, polysaccharides. Another form of a controlled release of the compounds of this invention is by a method based on the Oros therapeutic system (Alza Corp.), i.e., the drug is enclosed in a semipermeable membrane which allows water to enter and push drug out through a single small opening due to osmotic effects. Some enteric coatings also have a delayed release effect.

Other coatings may be used for the formulation. These include a variety of sugars which could be applied in a coating pan. The therapeutic agent could also be given in a film coated tablet and the materials used in this instance are divided into 2 groups. The first are the nonenteric materials and include methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, methylhydroxy-ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl-methyl cellulose, sodium carboxy-methyl cellulose, providone and the polyethylene glycols. The second group consists of the enteric materials that are commonly esters of phthalic acid.

A mix of materials might be used to provide the optimum film coating. Film coating may be carried out in a pan coater or in a fluidized bed or by compression coating.

Pulmonary delivery forms. Also contemplated herein is pulmonary  
5 delivery of the present protein (or derivatives thereof). The protein (or derivative) is delivered to the lungs of a mammal while inhaling and traverses across the lung epithelial lining to the blood stream. (Other reports of this include Adjei *et al.*, *Pharma. Res.* (1990) 7: 565-9; Adjei *et al.* (1990), *Internatl. J. Pharmaceutics* 63: 135-44 (leuprolide acetate); Braquet  
10 *et al.* (1989), *J. Cardiovasc. Pharmacol.* 13 (suppl.5): s.143-146 (endothelin-1); Hubbard *et al.* (1989), *Annals Int. Med.* 3: 206-12 ( $\alpha$ 1-antitrypsin); Smith *et al.* (1989), *J. Clin. Invest.* 84: 1145-6 ( $\alpha$ 1-proteinase); Oswein *et al.* (March 1990), "Aerosolization of Proteins", *Proc. Symp. Resp. Drug Delivery II*, Keystone, Colorado (recombinant human growth hormone); Debs *et al.*  
15 (1988), *J. Immunol.* 140: 3482-8 (interferon- $\gamma$  and tumor necrosis factor  $\alpha$ ) and Platz *et al.*, U.S. Patent No. 5,284,656 (granulocyte colony stimulating factor)).

Contemplated for use in the practice of this invention are a wide range of mechanical devices designed for pulmonary delivery of  
20 therapeutic products, including but not limited to nebulizers, metered dose inhalers, and powder inhalers, all of which are familiar to those skilled in the art. Some specific examples of commercially available devices suitable for the practice of this invention are the Ultravent nebulizer, manufactured by Mallinckrodt, Inc., St. Louis, Missouri; the  
25 Acorn II nebulizer, manufactured by Marquest Medical Products, Englewood, Colorado; the Ventolin metered dose inhaler, manufactured by Glaxo Inc., Research Triangle Park, North Carolina; and the Spinhaler powder inhaler, manufactured by Fisons Corp., Bedford, Massachusetts.

All such devices require the use of formulations suitable for the dispensing of the inventive compound. Typically, each formulation is specific to the type of device employed and may involve the use of an appropriate propellant material, in addition to diluents, adjuvants  
5 and/or carriers useful in therapy.

The inventive compound should most advantageously be prepared in particulate form with an average particle size of less than 10  $\mu\text{m}$  (or microns), most preferably 0.5 to 5  $\mu\text{m}$ , for most effective delivery to the distal lung.

10 Pharmaceutically acceptable carriers include carbohydrates such as trehalose, mannitol, xylitol, sucrose, lactose, and sorbitol. Other ingredients for use in formulations may include DPPC, DOPE, DSPC and DOPC. Natural or synthetic surfactants may be used. PEG may be used (even apart from its use in derivatizing the protein or analog).  
15 Dextrans, such as cyclodextran, may be used. Bile salts and other related enhancers may be used. Cellulose and cellulose derivatives may be used. Amino acids may be used, such as use in a buffer formulation.

Also, the use of liposomes, microcapsules or microspheres, inclusion complexes, or other types of carriers is contemplated.

20 Formulations suitable for use with a nebulizer, either jet or ultrasonic, will typically comprise the inventive compound dissolved in water at a concentration of about 0.1 to 25 mg of biologically active protein per mL of solution. The formulation may also include a buffer and a simple sugar (e.g., for protein stabilization and regulation of osmotic  
25 pressure). The nebulizer formulation may also contain a surfactant, to reduce or prevent surface induced aggregation of the protein caused by atomization of the solution in forming the aerosol.

Formulations for use with a metered-dose inhaler device will generally comprise a finely divided powder containing the inventive

compound suspended in a propellant with the aid of a surfactant. The propellant may be any conventional material employed for this purpose, such as a chlorofluorocarbon, a hydrochlorofluorocarbon, a hydrofluorocarbon, or a hydrocarbon, including trichlorofluoromethane, dichlorodifluoromethane, dichlorotetrafluoroethanol, and 1,1,1,2-tetrafluoroethane, or combinations thereof. Suitable surfactants include sorbitan trioleate and soya lecithin. Oleic acid may also be useful as a surfactant.

Formulations for dispensing from a powder inhaler device will comprise a finely divided dry powder containing the inventive compound and may also include a bulking agent, such as lactose, sorbitol, sucrose, mannitol, trehalose, or xylitol in amounts which facilitate dispersal of the powder from the device, e.g., 50 to 90% by weight of the formulation.

Nasal delivery forms. Nasal delivery of the inventive compound is also contemplated. Nasal delivery allows the passage of the protein to the blood stream directly after administering the therapeutic product to the nose, without the necessity for deposition of the product in the lung. Formulations for nasal delivery include those with dextran or cyclodextran. Delivery via transport across other mucous membranes is also contemplated.

Dosages. The dosage regimen involved in a method for treating the above-described conditions will be determined by the attending physician, considering various factors which modify the action of drugs, e.g. the age, condition, body weight, sex and diet of the patient, the severity of any infection, time of administration and other clinical factors. Generally, the daily regimen should be in the range of 0.1-1000 micrograms of the inventive compound per kilogram of body weight, preferably 0.1-150 micrograms per kilogram.



### Specific preferred embodiments

The inventors have determined preferred structures for the preferred peptides listed in Table 4 below. The symbol "Λ" may be any of the linkers described herein or may simply represent a normal peptide bond (i.e., so that no linker is present). Tandem repeats and linkers are shown separated by dashes for clarity.

**Table 4—Preferred embodiments**

| Sequence/structure   | SEQ ID NO: |
|--|------------|
| LPGCKWDLLIKQWVCDPL-Λ-V <sup>1</sup>                          | 44         |
| V <sup>1</sup> -Λ- LPGCKWDLLIKQWVCDPL                        | 45         |
| LPGCKWDLLIKQWVCDPL -Λ- LPGCKWDLLIKQWVCDPL -Λ-V <sup>1</sup>  | 46         |
| V <sup>1</sup> -Λ- LPGCKWDLLIKQWVCDPL -Λ- LPGCKWDLLIKQWVCDPL | 47         |
| SADCYFDILTKSDVCTSS-Λ-V <sup>1</sup>                          | 48         |
| V <sup>1</sup> -Λ- SADCYFDILTKSDVCTSS                        | 49         |
| SADCYFDILTKSDVTSS-Λ- SADCYFDILTKSDVTSS -Λ-V <sup>1</sup>     | 50         |
| V <sup>1</sup> -Λ- SADCYFDILTKSDVTSS -Λ- SADCYFDILTKSDVTSS   | 51         |
| FHDCKWDLLTKQWVCHGL-Λ-V <sup>1</sup>                          | 52         |
| V <sup>1</sup> -Λ- FHDCKWDLLTKQWVCHGL                        | 53         |
| FHDCKWDLLTKQWVCHGL -Λ- FHDCKWDLLTKQWVCHGL -Λ-V <sup>1</sup>  | 54         |
| V <sup>1</sup> -Λ- FHDCKWDLLTKQWVCHGL -Λ- FHDCKWDLLTKQWVCHGL | 55         |

"V<sup>1</sup>" is an Fc domain as defined previously herein. In addition to those listed in Table 4, the inventors further contemplate heterodimers in which each strand of an Fc dimer is linked to a different peptide sequence; for example, wherein each Fc is linked to a different sequence selected from Table 2.

All of the compounds of this invention can be prepared by methods described in PCT appl. no. WO 99/25044.

The invention will now be further described by the following working examples, which are illustrative rather than limiting.

## EXAMPLE 1

### Peptides

#### 5 Peptide Phage Display

##### 1. Magnetic bead preparation

###### A. Fc-TALL-1 immobilization on magnetic beads

The recombinant Fc-TALL-1 protein was immobilized on the Protein A Dynabeads (Dyna) at a concentration of 8  $\mu\text{g}$  of Fc-TALL-1 per 100  $\mu\text{l}$  of the  
10 bead stock from the manufacturer. By drawing the beads to one side of a tube using a magnet and pipetting away the liquid, the beads were washed twice with the phosphate buffer saline (PBS) and resuspended in PBS. The Fc-TALL-1 protein was added to the washed beads at the above concentration and incubated with rotation for 1 hour at room temperature. The Fc-TALL-1 coated beads were  
15 then blocked by adding bovine serum albumin (BSA) to 1% final concentration and incubating overnight at 4 °C with rotation. The resulting Fc-TALL-1 coated beads were then washed twice with PBST (PBS with 0.05% Tween-20) before being subjected to the selection procedures.

###### B. Negative selection bead preparation

20 Additional beads were also prepared for negative selections. For each panning condition, 250  $\mu\text{l}$  of the bead stock from the manufacturer was subjected to the above procedure (section 1A) except that the incubation step with Fc-TALL-1 was omitted. In the last washing step, the beads were divided into five 50  $\mu\text{l}$  aliquots.

##### 25 2. Selection of TALL-1 binding phage

###### A. Overall strategy

Two filamentous phage libraries, TN8-IX ( $5 \times 10^9$  independent transformants) and TN12-I ( $1.4 \times 10^9$  independent transformants) (Dyax Corp.), were used to select for TALL-1 binding phage. Each library was subjected to  
30 either pH 2 elution or 'bead elution' (section 2E). Therefore, four different panning conditions were carried out for the TALL-1 project (TN8-IX using the

pH2 elution method, TN8-IX using the bead elution method, TN12-I the using pH2 elution method, and TN12-I using the bead elution method). Three rounds of selection were performed for each condition.

#### B. Negative selection

5 For each panning condition, about 100 random library equivalent ( $5 \times 10^{11}$  pfu for TN8-IX and  $1.4 \times 10^{11}$  pfu for TN12-I) was aliquoted from the library stock and diluted to 300  $\mu$ l with PBST. After the last washing liquid was drawn out from the first 50  $\mu$ l aliquot of the beads prepared for negative selections (section 1B), the 300  $\mu$ l diluted library stock was added to the beads. The resulting  
10 mixture was incubated for 10 minutes at room temperature with rotation. The phage supernatant was drawn out using the magnet and added to the second 50  $\mu$ l aliquot for another negative selection step. In this way, five negative selection steps were performed.

#### C. Selection using the Fc-TALL-1 protein coated beads

15 The phage supernatant after the last negative selection step (section 1B) was added to the Fc-TALL-1 coated beads after the last washing step (section 1A). This mixture was incubated with rotation for two hours at room temperature, allowing specific phage to bind to the target protein. After the supernatant is discarded, the beads were washed seven times with PBST.

#### 20 D. pH2 elution of bound phage

After the last washing step (section 2C), the bound phages were eluted from the magnetic beads by adding 200  $\mu$ l of CBST (50 mM sodium citrate, 150 mM sodium chloride, 0.05% Tween-20, pH2). After 5 minute incubation at room temperature, the liquid containing the eluted phage were drawn out and transferred  
25 to another tube. The elution step was repeated again by adding 200  $\mu$ l of CBST and incubating for 5 minutes. The liquids from two elution steps were added together, and 100  $\mu$ l of 2 M Tris solution (pH 8) was added to neutralize the pH. 500  $\mu$ l of Min A Salts solution (60 mM  $K_2HPO_4$ , 33 mM  $KH_2PO_4$ , 7.6 mM  $(NH_4)SO_4$ , and 1.7 mM sodium citrate) was added to make the final volume to 1  
30 ml.

#### E. 'bead elution'

After the final washing liquid was drawn out (section 2C), 1 ml of Min A salts solution was added to the beads. This bead mixture was added directly to a concentrated bacteria sample for infection (section 3A and 3B).

### 5        3. Amplification

#### A. Preparation of plating cells

Fresh E. Coli. (XL-1 Blue MRF) culture was grown to  $OD_{600} = 0.5$  in LB media containing 12.5 µg/ml tetracycline. For each panning condition, 20 ml of this culture was chilled on ice and centrifuged. The bacteria pellet was  
10        resuspended in 1 ml of the Min A Salts solution.

#### B. Transduction

Each mixture from different elution methods (section 2D and 2E) was added to a concentrated bacteria sample (section 3A) and incubated at 37 °C for 15 minutes. 2 ml of NZCYM media (2XNZCYM, 50 µg/ml ampicillin) was  
15        added to each mixture and incubated at room temperature for 15 minutes. The resulting 4 ml solution was plated on a large NZCYM agar plate containing 50 µg/ml ampicillin and incubated overnight at 37 °C.

#### C. Phage Harvesting

Each of the bacteria/phage mixture that was grown overnight on a large  
20        NZCYM agar plate (section 3B) was scraped off in 35 ml of LB media, and the agar plate was further rinsed with additional 35 ml of LB media. The resulting bacteria/phage mixture in LB media was centrifuged to pellet the bacteria away. 50 ml of the phage supernatant was transferred to a fresh tube, and 12.5 ml of PEG solution (20% PEG8000, 3.5M ammonium acetate) was added and incubated  
25        on ice for 2 hours to precipitate phages. Precipitated phages were centrifuged down and resuspended in 6 ml of the phage resuspension buffer (250 mM NaCl, 100 mM Tris pH8, 1 mM EDTA). This phage solution was further purified by centrifuging away the remaining bacteria and precipitating the phage for the second time by adding 1.5 ml of the PEG solution. After a centrifugation step, the  
30        phage pellet was resuspended in 400 µl of PBS. This solution was subjected to a final centrifugation to rid of remaining bacteria debris. The resulting phage

preparation was titered by a standard plaque formation assay (Molecular Cloning, Maniatis et al 3<sup>rd</sup> Edition).

4. Two more rounds of selection and amplification.

In the second round, the amplified phage ( $10^{10}$  pfu) from the first round  
5 (section 3C) was used as the input phage to perform the selection and  
amplification steps (sections 2 and 3). The amplified phage ( $10^{10}$  pfu) from the  
2<sup>nd</sup> round in turn was used as the input phage to perform 3<sup>rd</sup> round of selection and  
amplification (sections 2 and 3). After the elution steps (sections 2D and 2E) of  
the 3<sup>rd</sup> round, a small fraction of the eluted phage was plated out as in the plaque  
10 formation assay (section 3C). Individual plaques were picked and placed into 96  
well microtiter plates containing 100  $\mu$ l of TE buffer in each well. These master  
plates were incubated in a 37 °C incubator for 1 hour to allow phages to elute into  
the TE buffer.

5. Clonal analysis (Phage ELISA and sequencing)

15 The phage clones were analyzed by phage ELISA and sequencing  
methods. The sequences were ranked based on the combined results from these  
two assays.

A. Phage ELISA

An XL-1 Blue MRF<sup>+</sup> culture was grown until OD<sub>600</sub> reaches 0.5. 30  $\mu$ l of  
20 this culture was aliquoted into each well of a 96 well microtiter plate. 10  $\mu$ l of  
eluted phage (section 4) was added to each well and allowed to infect bacteria for  
15 min at room temperature. 130  $\mu$ l of LB media containing 12.5  $\mu$ g/ml of  
tetracycline and 50  $\mu$ g/ml of ampicillin was added to each well. The microtiter  
plate was then incubated overnight at 37 °C. The recombinant TALL-1 protein (1  
25  $\mu$ g/ml in PBS) was allowed to coat onto the 96-well Maxisorp plates (NUNC)  
overnight and 4°C. As a control, the recombinant Fc-Trail protein was coated  
onto a separate Maxisorp plate at the same molar concentration as the TALL-1  
protein.

On the following day, liquids in the protein coated Maxisorp plates were  
30 discarded, and each well was blocked with 300  $\mu$ l of 2% BSA solution at 37 °C

for one hour. The BSA solution was discarded, and the wells were washed three times with the PBST solution. After the last washing step, 50  $\mu$ l of PBST was added to each well of the protein coated Maxisorp plates. Each of the 50  $\mu$ l overnight cultures in the 96 well microtiter plate was transferred to the

5 corresponding wells of the TALL-1 coated plates as well as the control Fc-Trail coated plates. The 100  $\mu$ l mixtures in the two kinds of plates were incubated for 1 hour at room temperature. The liquid was discarded from the Maxisorp plates, and the wells were washed five times with PBST. The HRP-conjugated anti-M13 antibody (Pharmacia) was diluted to 1:7,500, and 100  $\mu$ l of the diluted solution

10 was added to each well of the Maxisorp plates for 1 hour incubation at room temperature. The liquid was again discarded and the wells were washed seven times with PBST. 100  $\mu$ l of tetramethylbenzidine (TMB) substrate (Sigma) was added to each well for the color reaction to develop, and the reaction was stopped with 50  $\mu$ l of the 5 N  $H_2SO_4$  solution. The  $OD_{450}$  was read on a plate

15 reader (Molecular Devices).

#### B. Sequencing of the phage clones.

For each phage clone, the sequencing template was prepared by a PCR method. The following oligonucleotide pair was used to amplify about 500 nucleotide fragment:

20 primer #1 (5'-CGGCGCAACTATCGGTATCAAGCTG-3') (SEQ ID NO: 56)  
and primer #2 (5'-CATGTACCGTAACACTGAGTTTCGTC-3'). (SEQ ID NO: 57)

The following mixture was prepared for each clone.

| Reagents                                | volume ( $\mu$ L) / tube |
|---|--------------------------|
| dH <sub>2</sub> O                       | 26.25                    |
| 50% glycerol                            | 10                       |
| 10B PCR Buffer (w/o MgCl <sub>2</sub> ) | 5                        |
| 25 mM MgCl <sub>2</sub>                 | 4                        |
| 10 mM dNTP mix                          | 1                        |
| 100 $\mu$ M primer 1                    | 0.25                     |
| 100 $\mu$ M primer 2                    | 0.25                     |
| Taq polymerase                          | 0.25                     |
| Phage in TE (section 4)                 | 3                        |
| <b>Final reaction volume</b>            | <b>50</b>                |

The thermocycler (GeneAmp PCR System 9700, Applied Biosystems) was used to run the following program: 94°C for 5 min; [94°C for 30 sec, 55°C for 30 sec, 72°C for 45 sec.]x30 cycles; 72°C for 7 min; cool to 4°C. The PCR product  
5 was checked by running 5 µl of each PCR reaction on a 1% agarose gel. The PCR product in the remaining 45 µl from each reaction was cleaned up using the QIAquick Multiwell PCR Purification kit (Qiagen), following the manufacturer's protocol. The resulting product was then sequenced using the ABI 377 Sequencer (Perkin-Elmer) following the manufacturer recommended protocol.

10 6. Sequence ranking and consensus sequence determination

A. Sequence ranking

The peptide sequences that were translated from variable nucleotide sequences (section 5B) were correlated to ELISA data. The clones that showed high OD<sub>450</sub> in the TALL-1 coated wells and low OD<sub>450</sub> in the Fc-Trail coated  
15 wells were considered more important. The sequences that occur multiple times were also considered important. Candidate sequences were chosen based on these criteria for further analysis as peptides or peptibodies. Five and nine candidate peptide sequences were selected from the TN8-IX and TN12-I libraries, respectively.

20 B. Consensus sequence determination

The majority of sequences selected from the TN12-I library contained a very conserved DBL motif. This motif was also observed in sequences selected from the TN8-IB library as well. Another motif, PFPWE (SEQ ID NO: 110) was also observed in sequences obtained from the TN8-IB library.

25 A consensus peptide, FHDCKWDLLTQWVCHGL (SEQ ID NO: 58), was designed based on the DBL motif. Since peptides derived from the TN12-I library were the most active ones, the top 26 peptide sequences based on the above ranking criteria (section 5A) were aligned by the DBL motif. The underlined "core amino acid sequence" was obtained by determining the amino  
30 acid that occur the most in each position. The two cysteines adjacent to the core

sequences were fixed amino acids in the TN12-I library. The rest of the amino acid sequence in the consensus peptide is taken from one of the candidate peptides, TALL-1-12-10 (Table 2, SEQ ID NO: 37). The peptide and peptibody that was derived from this consensus sequence were most active in the B cell proliferation assay.

## EXAMPLE 2

### Peptibodies

A set of 12 TALL-1 inhibitory peptibodies (Table 5) was constructed in which a monomer of each peptide was fused in-frame to the Fc region of human IgG1. Each TALL-1 inhibitory peptibody was constructed by annealing the pairs of oligonucleotides shown in Table 6 to generate a duplex encoding the peptide and a linker comprised of 5 glycine residues and one valine residue as an NdeI to SalI fragment. These duplex molecules were ligated into a vector (pAMG21-RANK-Fc, described herein) containing the human Fc gene, also digested with NdeI and SalI. The resulting ligation mixtures were transformed by electroporation into *E. coli* strain 2596 cells (GM221, described herein). Clones were screened for the ability to produce the recombinant protein product and to possess the gene fusion having the correct nucleotide sequence. A single such clone was selected for each of the peptibodies. The nucleotide and amino acid sequences of the fusion proteins are shown in Figure 4A through 4F.

**Table 5. Peptide sequences and oligonucleotides used to generate TALL-1 inhibitory peptibodies.**

| Peptibody     | Peptibody<br>SEQ ID<br>NO | Peptide Sequence   | Sense<br>oligo-<br>nucleotide | Antisense<br>oligo-<br>nucleotide |
|---------------|---------------------------|--------------------|-------------------------------|-----------------------------------|
| TALL-1-8-1-a  | 29                        | PGTCFPPFPWECTHA    | 2517-24                       | 2517-25                           |
| TALL-1-8-2-a  | 30                        | WGACWPPFPWECFKE    | 2517-26                       | 2517-27                           |
| TALL-1-8-4-a  | 31                        | VPFCDLLTKHCFEA     | 2517-28                       | 2517-29                           |
| TALL-1-12-4-a | 32                        | GSRCYKQWDVLTKQCFHH | 2517-30                       | 2517-31                           |
| TALL-1-12-3-a | 33                        | LPGCKWDLLIKQWVCDPL | 2517-32                       | 2517-33                           |
| TALL-1-12-5-a | 34                        | SADCYFDILTKSDVCTSS | 2517-34                       | 2517-35                           |
| TALL-1-12-8-a | 35                        | SDDCMYDQLTRMFICSNL | 2517-36                       | 2517-37                           |
| TALL-1-12-9-a | 36                        | DLNCKYDELTYKEWCQFN | 2521-92                       | 2521-93                           |



|                  |    |                     |         |         |
|------------------|----|---------------------|---------|---------|
| TALL-1-12-10-a   | 37 | FHDCKYDLLTRQMVCHGL  | 2521-94 | 2521-95 |
| TALL-1-12-11-a   | 38 | RNHCFWDHLLKQDPCPSP  | 2521-96 | 2521-97 |
| TALL-1-12-14-a   | 39 | ANQCWWDLSLTKKNVCEFF | 2521-98 | 2521-99 |
| TALL-1-consensus | 58 | FHDCKWDLTLTKQWVCHGL | 2551-48 | 2551-49 |

Table 5B TALL-1 inhibitory peptibodies.

| Peptibody     | Peptibody<br>SEQ ID<br>NO | Peptide Sequence   |  |   |   |
|---------------|---------------------------|--|--|---|---|
| TALL-1-8-1-a  | 111                       | MPGTCFPPFPW<br>VFLFPPKPKD<br>DGVEVHNAKT<br>KCKVSNKALP<br>KNQVSLTCLV<br>SDGSFFLYSK<br>SLSLSPGK  | ECTHAGGGGG<br>TLMISRTPEV<br>KPREEQYNST<br>APIEKTISKA<br>KGFYPSDIAV<br>LTVDKSRWQQ       | VDKTHTCPPC<br>TCVVVDVSHE<br>YRVVSVLTVL<br>KGQPREPQVY<br>EWESNGQPEN<br>GNVFSCSVMH  | PAPELLGGPS<br>DPEVKFNWYV<br>HQDWLNGKEY<br>TLPPSRDELTA<br>NYKTTTPPVL<br>EALHNHYTQK |
| TALL-1-8-2-a  | 112                       | MWGACWPPFPW<br>VFLFPPKPKD<br>DGVEVHNAKT<br>KCKVSNKALP<br>KNQVSLTCLV<br>SDGSFFLYSK<br>SLSLSPGK  | ECFKEGGGG<br>TLMISRTPEV<br>KPREEQYNST<br>APIEKTISKA<br>KGFYPSDIAV<br>LTVDKSRWQQ        | VDKTHTCPPC<br>TCVVVDVSHE<br>YRVVSVLTVL<br>KGQPREPQVY<br>EWESNGQPEN<br>GNVFSCSVMH  | PAPELLGGPS<br>DPEVKFNWYV<br>HQDWLNGKEY<br>TLPPSRDELTA<br>NYKTTTPPVL<br>EALHNHYTQK |
| TALL-1-8-4-a  | 113                       | MVPFCDLLTK<br>VFLFPPKPKD<br>DGVEVHNAKT<br>KCKVSNKALP<br>KNQVSLTCLV<br>SDGSFFLYSK<br>SLSLSPGK   | HCFEAGGGGG<br>TLMISRTPEV<br>KPREEQYNST<br>APIEKTISKA<br>KGFYPSDIAV<br>LTVDKSRWQQ       | VDKTHTCPPC<br>TCVVVDVSHE<br>YRVVSVLTVL<br>KGQPREPQVY<br>EWESNGQPEN<br>GNVFSCSVMH  | PAPELLGGPS<br>DPEVKFNWYV<br>HQDWLNGKEY<br>TLPPSRDELTA<br>NYKTTTPPVL<br>EALHNHYTQK |
| TALL-1-12-4-a | 114                       | MGRCKYKWD<br>GGPSVFLFPP<br>NWYVDGVEVH<br>GKEYKCKVSN<br>DELTKNQVSL<br>PVLDSGDSFF<br>YTQKSLSLSP  | VLTKQCFHHG<br>KPKDTLMISR<br>NAKTKPREEQ<br>KALPAPIEKT<br>TCLVKGFYPS<br>LYSKLTVDKS<br>GK | GGGGVDKTHT<br>TPEVTCVVVD<br>YNSTYRVVSV<br>ISKAKGQPRE<br>DIAVEWESNG<br>RWQQGNVFSC  | CPPCPAPELL<br>VSHEDPEVKF<br>LTVLHQDWLN<br>PQVYTLPPSR<br>QPENNYKTTTP<br>SVMHEALHNH |
| TALL-1-12-3-a | 115                       | MLPGCKWDL<br>GGPSVFLFPP<br>NWYVDGVEVH<br>GKEYKCKVSN<br>DELTKNQVSL<br>PVLDSGDSFF<br>YTQKSLSLSP  | IKQWVCDPLG<br>KPKDTLMISR<br>NAKTKPREEQ<br>KALPAPIEKT<br>TCLVKGFYPS<br>LYSKLTVDKS<br>GK | GGGGVDKTHT<br>TPEVTCVVVD<br>YNSTYRVVSV<br>ISKAKGQPRE<br>DIAVEWESNG<br>RWQQGNVFSC  | CPPCPAPELL<br>VSHEDPEVKF<br>LTVLHQDWLN<br>PQVYTLPPSR<br>QPENNYKTTTP<br>SVMHEALHNH |
| TALL-1-12-5-a | 116                       | MSADCYFDIL<br>GGPSVFLFPP<br>NWYVDGVEVH<br>GKEYKCKVSN<br>DELTKNQVSL<br>PVLDSGDSFF<br>YTQKSLSLSP | TKSDVCTSSG<br>KPKDTLMISR<br>NAKTKPREEQ<br>KALPAPIEKT<br>TCLVKGFYPS<br>LYSKLTVDKS<br>GK | GGGG VDKTHT<br>TPEVTCVVVD<br>YNSTYRVVSV<br>ISKAKGQPRE<br>DIAVEWESNG<br>RWQQGNVFSC | CPPCPAPELL<br>VSHEDPEVKF<br>LTVLHQDWLN<br>PQVYTLPPSR<br>QPENNYKTTTP<br>SVMHEALHNH |
| TALL-1-12-8-a | 117                       | MSDDCMYDQL<br>GGPSVFLFPP<br>NWYVDGVEVH<br>GKEYKCKVSN<br>DELTKNQVSL                             | TRMFICSNLG<br>KPKDTLMISR<br>NAKTKPREEQ<br>KALPAPIEKT<br>TCLVKGFYPS                     | GGGGVDKTHT<br>TPEVTCVVVD<br>YNSTYRVVSV<br>ISKAKGQPRE<br>DIAVEWESNG                | CPPCPAPELL<br>VSHEDPEVKF<br>LTVLHQDWLN<br>PQVYTLPPSR<br>QPENNYKTTTP               |

|                               |     |   |  |   |  |
|-------------------------------|-----|---|--|---|--|
|                               |     | PVLDSGDSFF<br>YTQKSLSLSP  | LYSKLTVDKS<br>GK   | RWQQGNVFSC  | SVMHEALHNNH  |
| TALL-1-12-9-a                 | 118 | MDLNCKYDEL<br>GGPSVFLFPP<br>NWXVDGVEVH<br>GKEYKCKVSN<br>DELTKNQVSL<br>PVLDSGDSFF<br>YTQKSLSLSP              | TYKEWCQFNG<br>KPKDTLMISR<br>NAKTKPREEQ<br>KALPAPIEKT<br>TCLVKGFYPS<br>LYSKLTVDKS<br>GK               | GGGGVDKTHT<br>TPEVTCVVVD<br>YNSTYRVVSV<br>ISKAKGQPRE<br>DIAVEWESNG<br>RWQQGNVFSC              | CPPCPAPELL<br>VSHEDPEVKF<br>LTVLHQDWLN<br>PQVYTLPPSR<br>QPENNYKTTP<br>SVMHEALHNNH              |
| TALL-1-12-10-a                | 119 | MFHDCKYDLL<br>GGPSVFLFPP<br>NWXVDGVEVH<br>GKEYKCKVSN<br>DELTKNQVSL<br>PVLDSGDSFF<br>YTQKSLSLSP              | TRQMVCHGLG<br>KPKDTLMISR<br>NAKTKPREEQ<br>KALPAPIEKT<br>TCLVKGFYPS<br>LYSKLTVDKS<br>GK               | GGGGVDKTHT<br>TPEVTCVVVD<br>YNSTYRVVSV<br>ISKAKGQPRE<br>DIAVEWESNG<br>RWQQGNVFSC              | CPPCPAPELL<br>VSHEDPEVKF<br>LTVLHQDWLN<br>PQVYTLPPSR<br>QPENNYKTTP<br>SVMHEALHNNH              |
| TALL-1-12-11-a                | 120 | MRNHCWFDHL<br>GGPSVFLFPP<br>NWXVDGVEVH<br>GKEYKCKVSN<br>DELTKNQVSL<br>PVLDSGDSFF<br>YTQKSLSLSP              | LKQDICPSPG<br>KPKDTLMISR<br>NAKTKPREEQ<br>KALPAPIEKT<br>TCLVKGFYPS<br>LYSKLTVDKS<br>GK               | GGGGVDKTHT<br>TPEVTCVVVD<br>YNSTYRVVSV<br>ISKAKGQPRE<br>DIAVEWESNG<br>RWQQGNVFSC              | CPPCPAPELL<br>VSHEDPEVKF<br>LTVLHQDWLN<br>PQVYTLPPSR<br>QPENNYKTTP<br>SVMHEALHNNH              |
| TALL-1-12-14-a                | 121 | MANQCWWDLSL<br>GGPSVFLFPP<br>NWXVDGVEVH<br>GKEYKCKVSN<br>DELTKNQVSL<br>PVLDSGDSFF<br>YTQKSLSLSP             | TKKNVCEFFG<br>KPKDTLMISR<br>NAKTKPREEQ<br>KALPAPIEKT<br>TCLVKGFYPS<br>LYSKLTVDKS<br>GK               | GGGGVDKTHT<br>TPEVTCVVVD<br>YNSTYRVVSV<br>ISKAKGQPRE<br>DIAVEWESNG<br>RWQQGNVFSC              | CPPCPAPELL<br>VSHEDPEVKF<br>LTVLHQDWLN<br>PQVYTLPPSR<br>QPENNYKTTP<br>SVMHEALHNNH              |
| TALL-1-consensus              | 122 | MFHDCKWDDL<br>GGPSVFLFPP<br>NWXVDGVEVH<br>GKEYKCKVSN<br>DELTKNQVSL<br>PVLDSGDSFF<br>YTQKSLSLSP              | TKQWVCHGLG<br>KPKDTLMISR<br>NAKTKPREEQ<br>KALPAPIEKT<br>TCLVKGFYPS<br>LYSKLTVDKS<br>GK               | GGGGVDKTHT<br>TPEVTCVVVD<br>YNSTYRVVSV<br>ISKAKGQPRE<br>DIAVEWESNG<br>RWQQGNVFSC              | CPPCPAPELL<br>VSHEDPEVKF<br>LTVLHQDWLN<br>PQVYTLPPSR<br>QPENNYKTTP<br>SVMHEALHNNH              |
| TALL-1 12-3 tandem dimer      | 123 | MLPGCKWDDL<br>HMLPGCKWDL<br>LGGPSVFLFP<br>FNWYVDGVEV<br>NGKEYKCKVS<br>RDELTKNQVS<br>PPVLDSGDSF<br>HYTQKSLSL | IKQWVCDPLG<br>LIKQWVCDPL<br>KPKDTLMIS<br>HNAKTKPREE<br>NKALPAPIEK<br>LTCLVKGFYP<br>FLYSKLTVDK<br>PGK | SGSATGGSGS<br>GGGGVDKTH<br>RTPEVTCVVV<br>QYNSTYRVVS<br>TISKAKGQPR<br>SDIAVEWESN<br>SRWQQGNVFS | TASSGSGSAT<br>TCPPCPAPEL<br>DVSHEDPEVK<br>VLTVLHQDWL<br>EPQVYTLPPS<br>GQPENNYKTT<br>CSVMHEALHN |
| TALL-1 consensus tandem dimer | 124 | MFHDCKWDDL<br>HMFHDCKWDL<br>LGGPSVFLFP<br>FNWYVDGVEV<br>NGKEYKCKVS<br>RDELTKNQVS<br>PPVLDSGDSF<br>HYTQKSLSL | TKQWVCHGLG<br>LTKQWVCHGL<br>KPKDTLMIS<br>HNAKTKPREE<br>NKALPAPIEK<br>LTCLVKGFYP<br>FLYSKLTVDK<br>PGK | SGSATGGSGS<br>GGGGVDKTH<br>RTPEVTCVVV<br>QYNSTYRVVS<br>TISKAKGQPR<br>SDIAVEWESN<br>SRWQQGNVFS | TASSGSGSAT<br>TCPPCPAPEL<br>DVSHEDPEVK<br>VLTVLHQDWL<br>EPQVYTLPPS<br>GQPENNYKTT<br>CSVMHEALHN |

Table 6. Sequences of oligonucleotides used in peptibody construction.

| Oligo-nucleotide ID number | SEQ ID NO | Sequence   |
|----------------------------|-----------|--|
| 2517-24                    | 71        | TAT GCC GGG TAC TTG TTT CCC GTT CCC GTG GGA ATG CAC<br>TCA CGC TGG TGG AGG CGG TGG GG                    |
| 2517-25                    | 72        | TCG ACC CCA CCG CCT CCT GGA GCG TGA GTG CAT TCC CAC<br>GGG AAG CCG AAA CAA GTA CCC GGC A                 |
| 2517-26                    | 73        | TAT GTG GGG TGC TTG TTG GCC GTT CCC GTG GGA ATG TTT<br>CAA AGA AGG TGG AGG CGG TGG GG                    |
| 2517-27                    | 74        | TCG ACC CCA CCG CCT CCA CCT TCT TTG AAA CAT TCC<br>CACGGG AAC GGC CAA CAAGCA CCC CAC A                   |
| 2517-28                    | 75        | TAT GGT TCC GTT CTG TGA CCT GCT GAC TAA ACA CTG TTT<br>CGA AGC TGG TGG AGG CGG TGG GG                    |
| 2517-29                    | 76        | TCG ACC CCA CCG CCT CCA CCA GCT TCG AAA CAG TGT TTA<br>GTC AGC AGG TCA CAGAAC GGA ACC A                  |
| 2517-30                    | 77        | TAT GGG TTC TCG TTG TAA ATA CAA ATG GGA CGT TCT GAC<br>TAA ACA GTG TTT CCA CCA CGG TGG AGG CGG TGG GG    |
| 2517-31                    | 78        | TCG ACC CCA CCG CCT CCA CCG TGG TGG AAA CAC TGT TTA<br>GTC AGA ACG TCC CAT TTG TAT TTA CAA CGA GAA CCC A |
| 2517-32                    | 79        | TAT GCT GCC GGG TTG TAA ATG GGA CCT GCT GAT CAA ACA<br>GTG GGT TTG TGA CCC GCT GGG TGG AGG CGG TGG GG    |
| 2517-33                    | 80        | TCG ACC CCA CCG CCT CCA CCC AGC GGG TCA CAA ACC CAC<br>TGT TTG ATC AGC AGG TCC CAT TTA CAA CCC GGC AGC A |
| 2517-34                    | 81        | TAT GTC TGC TGA CTG TTA CTT CGA CAT CCT GAC TAA ATC<br>TGA CGT TTG TAC TTC TTC TGG TGG AGG CGG TGG GG    |
| 2517-35                    | 82        | TCG ACC CCA CCG CCT CCA CCA GAA GAA GTA CAA ACG TCA<br>GAT TTA GTC AGG ATG TCG AAG TAA CAG TCA GCA GAC A |
| 2517-36                    | 83        | TAT GTC TGA CGA CTG TAT GTA CGA CCA GCT GAC TCG TAT<br>GTT CAT CTG TTC TAA CCT GGG TGG AGG CGG TGG GG    |
| 2517-37                    | 84        | TCG ACC CCA CCG CCT CCA CCC AGG TTA GAA CAG ATG AAC<br>ATA CGA GTC AGC TGG TCG TAC ATA CAG TCG TCA GAC A |
| 2521-92                    | 85        | TAT GGA CCT GAA CTG TAA ATA CGA CGA ACT GAC TTA CAA<br>AGA ATG GTG TCA GTT CAA CGG TGG AGG CGG TGG GG    |
| 25221-93                   | 86        | TCG ACC CCA CCG CCT CCA CCG TTG AAC TGA CAC CAT TCT<br>TTG TAA GTC AGTTCG TCG TAT TTA CAG TTC AGG TCC A  |
| 2521-94                    | 87        | TAT GTT CCA CGA CTG TAA ATA CGA CCT GCT GAC TCG TCA<br>GAT GGT TTG TCA CGG TCT GGG TGG AGG CGG TGG GG    |
| 2521-95                    | 88        | TCG ACC CCA CCG CCT CCA CCC AGA CCG TGA CAA ACC ATC<br>TGA CGA GTC AGC AGG TCG TAT TTA CAG TCG TGG AAC A |
| 2521-96                    | 89        | TAT GCG TAA CCA CTG TTT CTG GGA CCA CCT GCT GAA ACA  |

|         |    |  |
|---------|----|--|
|         |    | GGA CAT CTG TCC GTC TCC GGG TGG AGG CGG TGG GG   |
| 2521-97 | 90 | TCG ACC CCA CCG CCT CCA CCC GGA GAC GGA CAG ATG TCC<br>TGT TTC AGC AGG TGG TCC CAG AAA CAG TGG TTA CGC A |
| 2521-98 | 91 | TAT GGC TAA CCA GTG TTG GTG GGA CTC TCT GCT GAA AAA<br>AAA CGT TTG TGA ATT CTT CGG TGG AGG CGG TGG GG    |
| 2521-99 | 92 | TCG ACC CCA CCG CCT CCA CCG AAG AAT TCA CAA ACG TTT<br>TTT TTC AGC AGA GAG TCC CAC CAA CAC TGG TTA GCC A |
| 2551-48 | 93 | TAT GTT CCA CGA CTG CAA ATG GGA CCT GCT GAC CAA ACA<br>GTG GGT TTG CCA CGG TCT GGG TGG AGG CGG TGG GG    |
| 2551-49 | 94 | TCG ACC CCA CCG CCT CCA CCC AGA CCG TGG CAA ACC CAC<br>TGT TTG GTC AGC AGG TCC CAT TTG CAG TCG TGG AAC A |

### pAMG21-RANK-Fc vector

pAMG21. The expression plasmid pAMG21 (ATCC accession no. 98113) can be derived from the Amgen expression vector pCFM1656 (ATCC #69576) which in turn be derived from the Amgen expression vector system described in US Patent No. 4,710,473. The pCFM1656 plasmid can be derived from the described pCFM836 plasmid (U.S. Patent No. 4,710,473) by:

- destroying the two endogenous NdeI restriction sites by end filling with T4 polymerase enzyme followed by blunt end ligation;
- replacing the DNA sequence between the unique AatII and ClaI restriction sites containing the synthetic P<sub>L</sub> promoter with a similar fragment obtained from pCFM636 (patent No. 4,710,473) containing the P<sub>L</sub> promoter (see SEQ ID NO: 95 below); and
- substituting the small DNA sequence between the unique ClaI and KpnI restriction sites with the oligonucleotide having the sequence of SEQ ID NO: 96.

SEQ ID NO: 95:

AatII  
5' CTAATTCGCTCTCACCTACCAAACAATGCCCCCTGCAAAAAATAAATTCATAT-  
3' TGCAGATTAAGGCGAGAGTGGATGGTTTGTACGGGGGACGTTTTTATTTAAGTATA-  
  
-AAAAAACATACAGATAACCATCTGCGGTGATAAATTATCTCTGGCGGTGTTGACATAAA-  
-TTTTTGTATGTCTATTGGTAGACGCCACTATTTAATAGAGACCGCCACAACGTATTT-  
  
-TACCACTGGCGGTGATACTGAGCACAT 3'  
-ATGGTGACCGCCACTATGACTCGTGTAGC 5'  
ClaI

SEQ ID NO: 96:

5' CGATTGATTCTAGAAGGAGGAATAACATATGGTTAACGCGTTGGAATTCGGTAC  
 3' TAAACTAAGATCTTCTCCTTATTGTATACCAATTGCGCAACCTTAAGC 5'  
Clal KpnI

5 The expression plasmid pAMG21 can then be derived from pCFM1656 by making a series of site-directed base changes by PCR overlapping oligonucleotide mutagenesis and DNA sequence substitutions. Starting with the BglII site (plasmid bp # 180) immediately 5' to the plasmid replication promoter P<sub>copB</sub> and  
 10 proceeding toward the plasmid replication genes, the base pair changes are as shown in Table 7 below.

**Table 7—Base pair changes resulting in pAMG21**

|    | <u>pAMG21 bp #</u> | <u>bp in pCFM1656</u>     | <u>bp changed to in pAMG21</u> |
|----|--------------------|---------------------------|--------------------------------|
| 15 | # 204              | T/A                       | C/G                            |
|    | # 428              | A/T                       | G/C                            |
|    | # 509              | G/C                       | A/T                            |
|    | # 617              | --                        | insert two G/C bp              |
| 20 | # 679              | G/C                       | T/A                            |
|    | # 980              | T/A                       | C/G                            |
|    | # 994              | G/C                       | A/T                            |
|    | # 1004             | A/T                       | C/G                            |
|    | # 1007             | C/G                       | T/A                            |
| 25 | # 1028             | A/T                       | T/A                            |
|    | # 1047             | C/G                       | T/A                            |
|    | # 1178             | G/C                       | T/A                            |
|    | # 1466             | G/C                       | T/A                            |
|    | # 2028             | G/C                       | bp deletion                    |
| 30 | # 2187             | C/G                       | T/A                            |
|    | # 2480             | A/T                       | T/A                            |
|    | # 2499-2502        | <u>AGTG</u><br>TCAC       | <u>GTCA</u><br>CAGT            |
| 35 | # 2642             | <u>TCCGAGC</u><br>AGGCTCG | 7 bp deletion                  |
|    | # 3435             | G/C                       | A/T                            |
| 40 | # 3446             | G/C                       | A/T                            |
|    | # 3643             | A/T                       | T/A                            |

The DNA sequence between the unique AatII (position #4364 in pCFM1656) and SacII (position #4585 in pCFM1656) restriction sites is  
 45 substituted with the DNA sequence below (SEQ ID NO: 97):.

[AatII sticky end] 5' GCGTAACGTATGCATGGTCTCC-  
(position #4358 in pAMG21) 3' TGCACGCATTGCATACGTACCAGAGG-

5 -CCATGCGAGAGTAGGGAACTGCCAGGCATCAAATAAAACGAAAGGCTCAGTCGAAAGACT-  
-GGTACGCTCTCATCCCTTGACGGTCCGTAGTTTATTTTGCTTTCCGAGTCAGCTTTCTGA-

-GGGCCTTTTCGTTTATCTGTTGTTTGTGCGGTGAACGCTCTCCTGAGTAGGACAAATCCGC-  
-CCCGGAAAGCAAAATAGACAACAAACAGCCACTTGCAGAGAGGACTCATCTGTTTAGGCG-

10 -CGGGAGCGGATTGTAACGTTGCGAAGCAACGGCCCCGAGGGTGGCGGGCAGGACGCCCCG-  
-GCCCTCGCCTAAACTTGCAACGCTTCGTTGCCGGGCCTCCACCGCCCCGTCTGCGGGCG-

-CATAAATGCCAGGCATCAAATTAAGCAGAAGGCCATCCTGACGGATGGCCTTTTTTGCGT-  
-GTATTTGACGGTCCGTAGTTTAATTTCGTCTTCCGGTAGGACTGCCTACCGGAAAAACGCA-

15

AatII

-TTCTACAACTCTTTTGTTTATTTTCTAAATACATTCAAATATGGACGTCGTACTTAAC-  
-AAGATGTTTGAGAAAACAAATAAAAAGATTTATGTAAGTTTATACCTGCAGCATGAATTG-

20 -TTTTAAAGTATGGGCAATCAATTGCTCCTGTTAAATTGCTTTAGAAATACTTTGGCAGC-  
-AAAATTTTCATACCCGTTAGTTAACGAGGACAATTTTAACGAAATCTTTATGAAACCGTCG-

-GGTTTGTGTTGATTGAGTTTCATTTGCGCATTTGGTTAAATGGAAGTGACCGTGCGCTTAC-  
-CCAAACAACATAAATCAAGTAAACGCGTAACCAATTTACCTTTCACTGGCACGCGAATG-

25 -TACAGCCTAATATTTTTGAAATATCCCAAGAGCTTTTTCTTCGCATGCCCACGCTAAAC-  
-ATGTCGGATTATAAAAACTTTATAGGGTTCTCGAAAAAGGAAGCGTACGGGTGCGATTG-

-ATTCTTTTTCTCTTTTGTTAAATCGTTGTTGATTATTATTTGCTATATTTATTTTTC-  
30 -TAAGAAAAAGAGAAAACCAATTTAGCAACAACTAAATAATAAACGATATAAATAAAAAG-

-GATAATTATCAACTAGAGAAGGAACAATTAATGGTATGTTTCATACACGCATGTAAAAATA-  
-CTATTAATAGTTGATCTCTTCTTGTTAATTACCATAACAAGTATGTGCGTACATTTTAT-

35 -AACTATCTATATAGTTGTCTTTCTCTGAATGTGCAAACTAAGCATTCGGAAGCCATTAT-  
-TTGATAGATATATCAACAGAAAGAGACTTACACGTTTTGATTTCGTAAGGCTTCGGTAATA-

-TAGCAGTATGAATAGGGAACTAAACCCAGTGATAAGACCTGATGATTTTCGCTTCTTTAA-  
40 -ATCGTCATACTTATCCCTTTGATTTGGGTCACTATTCTGGACTACTAAAGCGAAGAAATT-

-TTACATTTGGAGATTTTTTATTTACAGCATTGTTTTCAAATATATTCCAATTAATCGGTG-  
-AATGTAAACCTCTAAAAAATAAATGTGCGTAACAAAAGTTTATATAAGGTAAATTAGCCAC-

45 -AATGATTGGAGTTAGAATAATCTACTATAGGATCATATTTTATTAAATTAGCGTCATCAT-  
-TTACTAACCTCAATCTTATTAGATGATATCCTAGTATAAAATAATTTAATCGCAGTAGTA-

-AATATTGCCTCCATTTTTTAGGGTAATTATCCAGAATTGAAATATCAGATTTAACCATAG-  
-TTATAACGGAGGTAAAAAATCCCATTAATAGGCTTTAACTTTATAGTCTAAATTGGTATC-

50 -AATGAGGATAAATGATCGCGAGTAAATAATATTCACAATGTACCATTTTAGTCATATCAG-  
-TTACTCCTATTTACTAGCGCTCATTTATTATAAGTGTACATGGTAAATCAGTATAGTC-

-ATAAGCATTGATTAATATCATTATTGCTTCTACAGGCTTTAATTTTATTAATTATTCTGT-  
55 -TATTCGTAACATAATTATAGTAATAACGAAGATGTCCGAAATTAATAATAAAGACA-

-AAGTGTGTCGCGCATTTATGTCTTTCATACCCATCTCTTTATCCTTACCTATTGTTTGTC-  
-TTCACAGCAGCCGTAAATACAGAAAGTATGGGTAGAGAAATAGGAATGGATAACAAACAG-

60 -GCAAGTTTTGCGTGTTATATATCATTAACCGGTAATAGATTGACATTTGATTCTAATAA-  
-CGTTCAAACGCACAATATATAGTAATTTGCCATTATCTAACTGTAAACTAAGATTATT-

-ATTGGATTTTTGTCACACTATTATATCGCTTGAAATACAATTGTTTAACATAAGTACCTG-  
-TAACCTAAAAACAGTGTGATAATATAGCGAACTTTATGTTAACAAATTGTATTTCATGGAC-

The ribosome binding site of the cI857s7 gene has been modified to  
40 include an enhanced RBS. It has been inserted into the ebg operon between

nucleotide position 1170 and 1411 as numbered in Genbank accession number M64441Gb\_Ba with deletion of the intervening ebg sequence. The sequence of the insert is shown below with lower case letters representing the ebg sequences flanking the insert shown below (SEQ ID NO: 98):

5

```

ttatttctgGCGGCCGCACCATTATCACCGCCAGAGGTAAACTAGTCAACACGCACGGTGTTAGATAT
TTATCCCTTGCGGTGATAGATTGAGCACATCGATTGATTCTAGAAGGAGGGATAATATATGAG
CACAAAAAAGAAACCATTAACACAAGAGCAGCTTGAGGACGCACGTGCGCTTAAAGCAATTTA
10 TGAaaaaaAGAAAAATGAACTTGCGTTATCCAGGAATCTGTGCGAGACAAGATGGGGATGGG
GCAGTCAGGCGTTGGTGCTTTATTTAATGGCATCAATGCATTAAATGCTTATAACGCCGCATTGC
TTACAAAAATTCTCAAAGTTAGCGTTGAAGAAATTTAGCCCTTCAATCGCCAGAGAATCTACGAG
ATGTATGAAGCGGTTAGTATGCAGCCGTCACCTTAGAAGTGAGTATGAGTACCCTGTTTTTCTCA
TGTTACAGGCAGGGATGTTCTCACCTAAGCTTAGAACCTTTACCAAAGGTGATGCGGAGAGATGG
GTAAGCACAAACCAAAAAAGCCAGTGATTCTGCATTCTGGCTTGAGGTTGAAGGTAATTCATGA
15 CCGCACCAACAGGCTCCAAGCCAAGCTTTCCTGACGGAATGTTAATTCTCGTTGACCCTGAGCA
GGCTGTTGAGCCAGGTGATTTCTGCATAGCCAGACTTGGGGGTGATGAGTTTACCTTCAAGAAA
CTGATCAGGGATAGCGGTCAGGTGTTTTACAACCACTAAACCCACAGTACCCAATGATCCCAT
GCAATGAGAGTTGTTCCGTTGTGGGGAAAGTTATCGCTAGTCAGTGGCCTGAAGAGACGTTTGG
CTGATAGACTAGTGGATCCACTAGTgtttctgccc
20

```

The construct was delivered to the chromosome using a recombinant phage called MMeBg-cI857s7enhanced RBS #4 into F'tet/393. After recombination and resolution only the chromosomal insert described above remains in the cell. It was renamed F'tet/GM101. F'tet/GM101 was then modified

25 by the delivery of a  $\text{lacI}^Q$  construct into the ebg operon between nucleotide position 2493 and 2937 as numbered in the Genbank accession number M64441Gb\_Ba with the deletion of the intervening ebg sequence. The sequence of the insert is shown below with the lower case letters representing the ebg sequences flanking the insert (SEQ ID NO: 99) shown below:

30

```

ggcggaaaccGACGTCCATCGAATGGTGCAAAACCTTTCGCGGTATGGCATGATAGCGCCCGGAAGA
GAGTCAATTCAGGGTGGTGAATGTGAAACCAGTAACGTTATACGATGTGCGAGAGTATGCCGGT
GTCTCTTATCAGACCGTTTCCCGCGTGGTGAACCAGGCCAGCCACGTTTCTGCGAAAACGCGGG
35 AAAAAAGTCGAAGCGGCGATGGCGGAGCTGAATTACATTCCCAACCGCGTGGCACAACAAGTGG
CGGGCAAACAGTCGCTCCTGATTGGCGTTGCCACCTCCAGTCTGGCCCTGCACGCGCGCTCGCA
AATTGTGCGGCGGATTAATCTCGCGCCGATCAACTGGGTGCCAGCGTGGTGGTGTGATGGTA
GAACGAAGCGGCGTGAAGCCTGTAAAGCGGCGGTGCACAATCTTCTCGCGCAACGCGTCAGTG
GGCTGATCATTAACTATCCGCTGGATGACCAGGATGCCATTGCTGTGGAAGCTGCCTGCACTAA
40 TGTTCCGGCGTTATTTCTTGATGTCTTGACCAAGACACCCATCAACAGTATTATTTCTCCCATGA
AGACGGTACGCGACTGGGCGTGGAGCATCTGGTGCATTGGGTACCAGCAAATCGCGCTGTTA
GCGGGCCCATTAAGTTCTGTCTCGGCGCTGCGTCTGGCTGGCTGGCATAAATATCTCACTCG
CAATCAAATTCAGCCGATAGCGGAACGGGAAGGCGACTGGAAGTCCATGTCCGGTTTTCAACAA
ACCATGCAAAATGCTGAATGAGGGCATCGTTCCCACTGCGATGCTGGTTGCCAACGATCAGATGG
CGCTGGGCGCAATGCGCGCCATTACCGAGTCCGGCTGCGCGTTGGTGCGGATATCTCGGTAGT
45 GGGATACGACGATACCGAAGACAGCTCATGTTATATCCCGCCGTTAACCACCATCAAAACAGGAT
TTTCGCTGCTGGGGCAAACCAGCGTGGACCGCTTGGTCAACTCTCTCAGGGCCAGGCGGTGA

```



AGGGCAATCAGCTGTTGCCGCTCACTGGTGAAAAGAAAAACCACCCTGGCGCCCAATACGCA  
 AACCGCTCTCCCGCGCGTTGGCCGATTCAATATGCAGCTGGCACGACAGGTTCCCGACTGG  
 AAAGCGGACAGTAAGGTACCATAGGATCCaggcacagga

5           The construct was delivered to the chromosome using a recombinant  
 phage called AGebg-LacIQ#5 into F'tet/GM101. After recombination and  
 resolution only the chromosomal insert described above remains in the cell. It  
 was renamed F'tet/GM221. The F'tet episome was cured from the strain using  
 acridine orange at a concentration of 25 µg/ml in LB. The cured strain was  
 10 identified as tetracycline sensitive and was stored as GM221.

Expression in E. coli. Cultures of each of the pAMG21-Fc-fusion  
 constructs in E. coli GM221 were grown at 37 °C in Luria Broth medium.  
 Induction of gene product expression from the luxPR promoter was achieved  
 15 following the addition of the synthetic autoinducer N-(3-oxohexanoyl)-DL-  
 homoserine lactone to the culture media to a final concentration of 20 ng/ml.  
 Cultures were incubated at 37 °C for a further 3 hours. After 3 hours, the bacterial  
 cultures were examined by microscopy for the presence of inclusion bodies and  
 were then collected by centrifugation. Refractile inclusion bodies were observed  
 20 in induced cultures indicating that the Fc-fusions were most likely produced in the  
 insoluble fraction in E. coli. Cell pellets were lysed directly by resuspension in  
 Laemmli sample buffer containing 10% β-mercaptoethanol and were analyzed by  
 SDS-PAGE. In each case, an intense Coomassie-stained band of the appropriate  
 molecular weight was observed on an SDS-PAGE gel.

25

### EXAMPLE 3

#### TALL-1 peptibody inhibits TALL-1 mediated B cell proliferation

Mouse B lymphocytes were isolated from C57BL/6 spleens by negative  
 selection. (MACS CD43 (Ly-48) Microbeads, Miltenyi Biotech, Auburn, CA).  
 30 Purified ( $10^5$ ) B cells were cultured in MEM, 10% heat inactivated FCS,  $5 \times 10^{-5}$ M  
 2-mercaptoethanol, 100 U/ml penicillin, 100 µg/ml streptomycin) in triplicate in  
 96-well flat bottom tissue culture plates with 10 ng/ml TALL-1 protein and 2  
 µg/ml of Goat F(ab')<sub>2</sub> anti-mouse IgM (Jackson ImmunoResearch Laboratory,

West Grove, Pennsylvania) with the indicated amount of recombinant TALL-1 peptibody for a period of 4 days at 37 °C, 5%CO<sub>2</sub>. Proliferation was measured by the uptake of radioactive <sup>3</sup>[H] thymidine after an 18-hour incubation period.

5

#### EXAMPLE 4

##### TALL-1 peptibody blocks TALL-1 binding to its receptors

Reacti-Gel 6x (Pierce) were pre-coated with human AGP3 (also known as TALL-1, Khare et al., Proc. Natl. Acad. Sci. 97:3370-3375, 2000) and blocked  
10 with BSA. 100 pM and 40 pM of AGP3 peptibody samples were incubated with indicated various concentrations of human AGP3 at room temperature for 8 hours before run through the human AGP3-coated beads. The amount of the bead-bound peptibody was quantified by fluorescent (Cy5) labeled goat anti-human-Fc antibody (Jackson Immuno Research). The binding signal is proportional to the  
15 concentration of free peptibody at binding equilibrium. Dissociation equilibrium constant ( $K_D$ ) was obtained from nonlinear regression of the competition curves using a dual-curve one-site homogeneous binding model (KinEx™ software).  $K_D$  is about 4 pM for AGP3 peptibody (SEQ ID NO: 123) binding with human AGP3 (Figure 10).

20 To determine if this AGP3 peptibody can neutralize murine AGP3 binding as well as human AGP3, a BIAcore neutralizing assay was utilized. All experiments were performed on a BIAcore 3000 at room temperature. Human TACI-Fc protein (Xia et al, J. Exp. Med. 192, 137-144, 2000) was immobilized to a B1 chip using 10 mM Acetate pH 4.0 to a level of 2900RU. A blank flow cell  
25 was used as a background control. Using a running buffer of PBS (without calcium or magnesium) containing 0.005% P20, 1 nM recombinant human AGP3 (in running buffer plus, 0.1 mg/ml BSA) was incubated without and with indicated various amount of AGP3 peptibody (x axis) before injected over the surface of the receptor. Regeneration was performed using 8 mM glycine pH 1.5 for 1 minute,  
30 25 mM 3-[cyclohexylamino]-1-propanesulfonic acid (CAPS) pH 10.5, 1 M NaCl for 1 minute. For determination of murine AGP3 binding, human his-tagged

TACI was immobilized to 1000 RU in the above buffer. 5 nM recombinant murine AGP3 (in running buffer plus, 0.1 mg/ml BSA) was incubated without and with the various amounts indicated in Figure 11 of AGP3 peptibody (x axis) before injected over the surface of the receptor. Regeneration was performed with 10 mM HCl pH2, twice for 30 seconds. Relative binding of both human and murine AGP3 at presence vs absence of AGP3 peptibody (SEQ ID NO: 123) was measured (y axis). Relative binding response was determined as (RU-RU blank/ RUo-RU blank). The AGP3 peptibody (SEQ ID NO: 123) inhibited both human and murine AGP3 binding to its receptor TACI (Figures 11A and 11B).

To examine if this AGP3 peptibody blocks AGP3 binding to all three receptors (TACI, BCMA and BAFFR), recombinant soluble receptor TACI, BCMA and BAFFR proteins were immobilized to CM5 chip. Using 10 mM acetate, pH4, human TACI-Fc was immobilized to 6300 RU, human BCMA-Fc to 5000 RU, and BAFFR-Fc to 6000 RU. 1 nM of recombinant human AGP3 (in running buffer containing 0.1 mg/ml BSA and 0.1 mg/ml Heparin) or 1 nM recombinant APRIL protein (Yu, et al., Nat. Immunol., 1:252-256, 2000) were incubated with indicated amount of AGP3 peptibody before injection over each receptor surface. Regeneration for the AGP3 experiment was done with 8 mM glycine, pH 1.5, for 1 minute, followed by 25 mM CAPS, pH 10.5, 1M NaCl for 1 minute. Regeneration for the APRIL experiment was performed with 8 mM glycine, pH 2, for one minute, followed by 25 mM CAPS, pH 10.5, 1 M NaCl for one minute. Relative binding of AGP3 or APRIL was measured. AGP3 peptibody (SEQ ID NO: 123) blocked AGP3 binding to all three receptors (Figure 12A). AGP3 peptibody didn't affect APRIL binding to the receptors (Figure 12B).

## EXAMPLE 5

### AGP3 peptibody blocks AGP3 mediated B cell proliferation

Mouse B lymphocytes were isolated from C57BL/6 spleens by negative selection. (MACS CD43 (Ly-48) Microbeads, Miltenyi Biotech, Auburn, CA).

Purified ( $10^5$ ) B cells were cultured in minimal essential medium (MEM), 10% heat inactivated fetal calf serum (FCS),  $5 \times 10^{-5}$  M 2-mercaptoethanol, 100 U/ml penicillin, 100  $\mu$ g/ml streptomycin) in triplicate in 96-well flat bottom tissue culture plates with 10 ng/ml AGP3 (TALL-1) protein and 2  $\mu$ g/ml of Goat F(ab')<sub>2</sub> anti-mouse IgM (Jackson ImmunoResearch Laboratory, West Grove, Pennsylvania) with the indicated amount of recombinant AGP3 peptibody (SEQ ID NO: 123) for a period of 4 days at 37 °C, 5% CO<sub>2</sub>. Proliferation was measured by the uptake of radioactive <sup>3</sup>[H] thymidine after an 18-hour incubation period.

10

### EXAMPLE 6

#### AGP3 peptibody on AGP3-stimulated Ig production in mice

Mice (Balb/c females of 9-14 weeks of age and 19-21 g of weight) were purchased from Charles River Laboratories, Wilmington, MA. Mice (n = 10) were treated i.p. with 1 mg/Kg of human AGP3 once a day for five consecutive days followed by 5 mg/Kg or 0.5 mg/Kg of AGP3 peptibody (SEQ ID NO: 123) or by saline or by 5 mg/Kg of human Fc. Other mice were left untreated. Mice were sacrificed on the sixth day to measure serum IgM and IgA, which were measured by ELISA. Briefly, plates were coated with capture antibodies specific for IgM or IgA (Southern Biotechnology Associates, Birmingham, AL), blocked, and added with dilutions of standard (IgM from Calbiochem, San Diego, CA and IgA from Southern Biotechnology Associates) or test samples. Captured Ig were revealed using biotinylated antibodies specific for IgM or IgA (Southern Biotechnology Associates), neutravidin-conjugated peroxidase (Pierce, Rockford, IL), and tetramethylbenzidine (TMB) microwell peroxidase substrate (KPL, Gaithersburg, MD). Optical densities were quantitated in a Thermomax ELISA reader (Molecular Devices, Menlo Park, CA).

Human AGP3-stimulated increase in serum levels of IgM and IgA was blocked by 5 mg/Kg of the anti-AGP3 peptibody (SEQ ID NO: 123) and not by 0.5 mg/Kg (Figures 14A and 14B).

### EXAMPLE 7

#### AGP3 peptibody reduced spleen B cell number in mice

Mice (as above, n = 7) were treated i.p. for seven consecutive days with 5  
5 mg/Kg or 1.5 mg/Kg or 0.5 mg/Kg of AGP3 peptibody (SEQ ID NO: 123) or with  
saline or with 5 mg/Kg of human Fc. Mice were sacrificed on the eighth day to  
count spleen B cell number. Spleens were collected in saline and gently disrupted  
by manual homogenization to yield a cell suspension. The total cell number was  
obtained with a H1E counter (Technicon, Tarrytown, NY). Percentages of B cells  
10 were derived by immunofluorescence double staining and flow cytometry using  
fluorescein isothiocyanate (FITC)-conjugated and phycoerythrin (PE)-  
conjugated Ab against CD3 and B220, respectively (PharMingen, San Diego,  
CA) and a FACScan analyser (Becton and Dickinson, Mountain View, CA). B  
cells were identified for being CD3-B220+. At all doses, the AGP3 peptibody  
15 (SEQ ID NO: 123) decreased spleen B cell number in a dose-response fashion  
(Figure 14) (SEQ ID NO: 123).

### EXAMPLE 8

#### AGP3 peptibody reduced arthritis severity in mouse CIA model

20 Eight to 12 week old DBA/1 mice (obtained from Jackson Laboratories,  
Bar Harbor, ME) were immunized with bovine collagen type II (bCII) (purchased  
from University of Utah), emulsified in complete Freund's adjuvant (Difco)  
intradermally at the base of tail. Each injection was 100 µl containing 100 µg of  
25 bCII. Mice were boosted 3 weeks after the initial immunization with bCII  
emulsified in incomplete Freund's adjuvant. Treatment was begun from the day of  
booster immunization for 4 weeks. Mice were examined for the development of  
arthritis. As described before (Khare et al., *J. Immunol.* 155: 3653-9, 1995), all  
four paws were individually scored from 0-3. Therefore arthritis severity could  
30 vary from 0 to 12 for each animal. AGP3 (SEQ ID NO: 123) peptibody treatment  
significantly reduced the severity of arthritic scores (Figure 15).

Serum samples were taken one week after final treatment (day 35) for the analysis of anti-collagen antibody level. High binding ELISA plates (Immulon, Nunc) were coated with 50  $\mu$ l of 4  $\mu$ g/ml solution of bovine CII in carbonate buffer and plated were kept in cold overnight in the refrigerator. Plates were  
5 washed three times with cold water. 75  $\mu$ l of blocking solution made up of PBS/.05% tween 20/1% BSA was used to block non-specific binding for an hour. Samples were diluted (in blocking buffer) in dilution plates at 1:25, 1:100, 1:400, and 1:1600 and 25  $\mu$ l of these samples were added to each well of the ELISA plate for a final dilution of 100, 400, 1600, and 6400 with a final volume of 100  
10  $\mu$ l/well. After incubation at room temperature for 3 hours, plates were washed three times again. 100  $\mu$ l of secondary antibody diluted in blocking buffer (rat anti-mouse IgM, IgG2a, IgG2b, IgG1, IgG3-HRP) was added to each well and plates were incubated for at least 2 hours. Plates were washed four times. 100  $\mu$ l of TMB solution (Sigma) was added to each well and the reaction was stopped  
15 using 50  $\mu$ l of 25% sulfuric acid. Plates were read using an ELISA plate reader at 450 nm. OD was compared with a standard pool representing units/ml. AGP3 peptibody (SEQ ID NO: 123) treatment reduced serum anti-collagen II IgG1, IgG3, IgG2a, and IgG2b levels compared to PBS or Fc control treatment groups (Figure 16).

20

### EXAMPLE 9

#### Treatment of AGP3 peptibody in NZB/NZW lupus mice

Five month old lupus prone NZBx NZBWF1 mice were treated i.p.  
25 3X/week for 8 weeks with PBS or indicated doses of AGP3 peptibody or human Fc proteins. Prior to the treatment, animals were pre-screened for protein in the urine with Albustix reagents strips (Bayer AG). Mice having greater than 100 mg/dl of protein in the urine were not included in the study. Protein in the urine was evaluated monthly throughout the life of the experiment. AGP3 peptibody  
30 (SEQ ID NO: 123) treatment led to delay of proteinuria onset and improved survival (Figure 17).

AGP3 peptibody treatment reduced B cell number in mice. Balb/c mice received 7 daily intraperitoneal injections of indicated amount of AGP3 peptibody (SEQ ID NO: 123) or human Fc protein. On day 8, spleens were collected, and subject to FACS analysis for B220+ B cells as set for in Table 8.

5

**Table 8**  
**AGP3 Pb Reduces B Cell Number in Normal Mice**

| n=7       | dose (1/dayx7) | spleen B cell<br>(1x10e6) | SD  | t test      |
|-----------|----------------|---------------------------|-----|-------------|
| saline    |                | 51.3                      | 9.6 |             |
| Fc        | 5mg/Kg         | 45.5                      | 7.1 |             |
| Peptibody | 5mg/Kg         | 20.1                      | 3.8 | 1.37856E-05 |
|           | 1.5mg/Kg       | 22.6                      | 6.9 | 5.10194E-05 |
|           | 0.5mg/Kg       | 25.8                      | 3.6 | 0.000111409 |

10

\* \* \*

The invention now being fully described, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto, without departing from the spirit and scope of the invention as set forth herein.

15

**What is claimed is:**

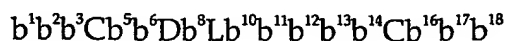
1. A TALL-1-binding composition of matter comprising an amino acid sequence  $Dz^2Lz^4$ , wherein  $z^2$  is an amino acid residue and  $z^4$  is T or I,  
 5 and wherein the composition of matter does not comprise a fragment of TACI, BCMA, or BAFFR (SEQ ID NOS: 195, 196, and 197).
2. The composition of matter of Claim 1, wherein  $z^4$  is T.
3. A TALL-1-binding composition of matter comprising an amino acid sequence  $Dz^2LI$ , wherein  $z^2$  is an amino acid residue.
- 10 4. The composition of matter of Claim 1 comprising an amino acid sequence of the formula



(SEQ. ID. NO: 100)

wherein:

- 15  $a^1, a^2, a^3$  are each independently absent or amino acid residues;  
 $a^6$  is an amino acid residue;  
 $a^8$  is T or I;  
 $a^9$  is a basic or hydrophobic residue;  
 $a^{12}$  is a neutral polar residue; and
- 20  $a^{13}$  and  $a^{14}$  are each independently absent or amino acid residues.
5. The composition of matter of Claim 4 wherein  $a^8$  is T and  $a^9$  is a basic residue.
6. The composition of matter of Claim 4 wherein  $a^9$  is K and  $a^{12}$  is F.
7. The composition of matter of Claim 1 comprising an amino acid  
 25 sequence of the formula



(SEQ. ID. NO: 104)

wherein:

- $b^1$  and  $b^2$  are each independently absent or amino acid residues;
- 30  $b^3$  is an acidic or amide residue;



b<sup>5</sup> is an amino acid residue;

b<sup>6</sup> is an aromatic residue;

b<sup>8</sup> is an amino acid residue;

b<sup>10</sup> is T or I;

5 b<sup>11</sup> is a basic residue;

b<sup>12</sup> and b<sup>13</sup> are each independently amino acid residues;

b<sup>14</sup> is a neutral polar residue; and

b<sup>16</sup>, b<sup>17</sup>, and b<sup>18</sup> are each independently absent or amino acid residues.

10 8. The composition of matter of Claim 7 wherein:

b<sup>3</sup> is D, Q, or E;

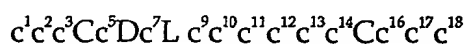
b<sup>6</sup> is W or Y;

b<sup>10</sup> is T;

b<sup>11</sup> is K or R; and

15 b<sup>14</sup> is V or L.

9. The composition of matter of Claim 1 comprising an amino acid sequence of the formula



(SEQ. ID. NO: 105)

20 wherein:

c<sup>1</sup>, c<sup>2</sup>, and c<sup>3</sup> are each independently absent or amino acid residues;

c<sup>5</sup> is an amino acid residue;

c<sup>7</sup> is an amino acid residue;

c<sup>9</sup> is T or I;

25 c<sup>10</sup> is a basic residue;

c<sup>11</sup> and c<sup>12</sup> are each independently amino acid residues;

c<sup>13</sup> is a neutral polar residue;

c<sup>14</sup> is an amino acid residue;

c<sup>16</sup> is an amino acid residue;

30 c<sup>17</sup> is a neutral polar residue; and

$c^{18}$  is an amino acid residue or is absent.

10. The composition of matter of Claim 9 wherein:

$c^9$  is T;

$c^{10}$  is K or R;

5  $c^{13}$  is a I, L, or V; and

$c^{17}$  is A or L.

11. The composition of matter of Claim 1 comprising an amino acid sequence of the formula



10 (SEQ. ID. NO: 106)

wherein:

$d^1$ ,  $d^2$ , and  $d^3$  are each independently absent or amino acid residues;

$d^5$ ,  $d^6$ , and  $d^7$  are each independently amino acid residues;

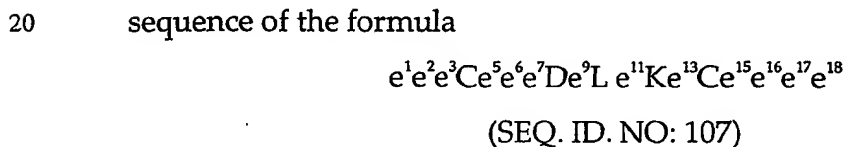
$d^{10}$  is an amino acid residue;

15  $d^{13}$  is T or I;

$d^{14}$  is an amino acid residue; and

$d^{16}$ ,  $d^{17}$ , and  $d^{18}$  are each independently absent or amino acid residues.

12. The composition of matter of Claim 1 comprising an amino acid sequence of the formula



wherein:

$e^1$ ,  $e^2$ , and  $e^3$  are each independently absent or amino acid residues;

25  $e^5$ ,  $e^6$ ,  $e^7$ ,  $e^9$ , and  $e^{13}$  are each independently amino acid residues;

$e^{11}$  is T or I; and

$e^{15}$ ,  $e^{16}$ , and  $e^{17}$  are each independently absent or amino acid residues.

13. The composition of matter of Claim 1 comprising an amino acid sequence of the formula



(SEQ ID NO: 109)

5 wherein:

$f^1$ ,  $f^2$ , and  $f^3$  are absent or are amino acid residues;

$f^{\delta}$  is W, Y, or F;

$f^7$  is an amino acid residue;

$f^9$  is T or I;

10  $f^{10}$  is K, R, or H;

$f^{12}$  is C, a neutral polar residue, or a basic residue (W, C, or R preferred);

$f^{13}$  is C, a neutral polar residue or is absent; and

$f^{14}$  is any amino acid residue or is absent;

15 provided that only one of  $f^1$ ,  $f^2$ , and  $f^3$  may be C, and only one of  $f^{12}$ ,  $f^{13}$ , and  $f^{14}$  may be C.

14. The composition of matter of Claim 13, wherein  $f^{\delta}$  is W.

15. The composition of matter of Claim 13, wherein  $f^7$  is L.

16. The composition of matter of Claim 13, wherein  $f^9$  is T.

20 17. The composition of matter of Claim 13, wherein  $f^{10}$  is K.

18. The composition of matter of Claim 13, wherein  $f^{12}$  is C and one of  $f^1$ ,  $f^2$ , and  $f^3$  is C.

19. The composition of matter of Claim 13, wherein  $f^{13}$  is V.

20. The composition of matter of Claim 13 comprising an amino acid  
25 sequence of the formula



(SEQ ID NO: 125).

21. The composition of matter of Claim 20 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 32, 33, 58,

60, 63, 66, 67, 69, 114, 115, 122, 123, 124, 147-150, 152-177, 179, 180, and 187.

22. The composition of matter of Claim 20 comprising an amino acid  
5 sequence of the formula

LPGCKWDLLIKQWVCDPL (SEQ ID NO: 33).

23. A composition of matter comprising an amino acid sequence of the  
formula

$$g^1 g^2 g^3 C g^5 P F g^8 W g^{10} C g^{11} g^{12} g^{13}$$

10 (SEQ. ID. NO: 101)

wherein:

- $g^1$ ,  $g^2$  and  $g^3$  are each independently absent or amino acid residues;  
 $g^5$  is a neutral polar residue;  
 $g^8$  is a neutral polar residue;  
15  $g^{10}$  is an acidic residue;  
 $g^{12}$  and  $g^{13}$  are each independently amino acid residues; and  
 $g^{14}$  is absent or is an amino acid residue.

24. The composition of matter of Claim 23 wherein:

- $g^2$  is G;  
20  $g^5$  is W;  
 $g^8$  is P;  
 $g^{10}$  is E; and  
 $g^{13}$  is a basic residue.

25. A composition of matter comprising an amino acid sequence of the  
25 formula

$$h^1 h^2 h^3 C W h^6 h^7 W G h^{10} C h^{12} h^{13} h^{14}$$

(SEQ. ID. NO: 102)

wherein:

- $h^1$ ,  $h^2$ , and  $h^3$  are each independently absent or amino acid residues;  
30  $h^6$  is a hydrophobic residue;

$h^7$  is a hydrophobic residue;

$h^{10}$  is an acidic or polar hydrophobic residue; and

$h^{12}$ ,  $h^{13}$ , and  $h^{14}$  are each independently absent or amino acid residues.

26. The composition of matter of Claim 25 wherein:

5  $h^1$  is G;

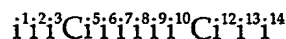
$h^6$  is A;

$h^7$  is a neutral polar residue; and

$h^{10}$  is an acidic residue.

27. A composition of matter comprising an amino acid sequence of the

10 formula



(SEQ. ID. NO: 103)

wherein:

$i^1$  is absent or is an amino acid residue;

15  $i^2$  is a neutral polar residue;

$i^3$  is an amino acid residue;

$i^5$ ,  $i^6$ ,  $i^7$ , and  $i^8$  are each independently amino acid residues;

$i^9$  is an acidic residue;

$i^{10}$  is an amino acid residue;

20  $i^{12}$  and  $i^{13}$  are each independently amino acid residues; and

$i^{14}$  is a neutral polar residue.

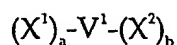
28. The composition of matter of Claim 27 wherein:

$i^2$  is W; and

$i^{14}$  is W.

25 29. A TALL-1 binding composition of matter comprising an amino acid sequence of the formula PFPWE (SEQ ID NO: 110). :

30. The composition of matter of Claim 1 having the formula



and multimers thereof, wherein:

$V^1$  is a vehicle;

$X^1$  and  $X^2$  are each independently selected from  $-(L^1)_c-P^1$ ,

$-(L^1)_c-P^1-(L^2)_d-P^2$ ,  $-(L^1)_c-P^1-(L^2)_d-P^2-(L^3)_e-P^3$ , and

$-(L^1)_c-P^1-(L^2)_d-P^2-(L^3)_e-P^3-(L^4)_f-P^4$

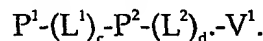
5 one or more of  $P^1$ ,  $P^2$ ,  $P^3$ , and  $P^4$  each independently comprise

$Dz^2Lz^4$ ;

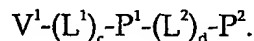
$L^1$ ,  $L^2$ ,  $L^3$ , and  $L^4$  are each independently linkers; and

a, b, c, d, e, and f are each independently 0 or 1, provided that at least one of a and b is 1.

10 31. The composition of matter of Claim 30 of the formula



32. The composition of matter of Claim 30 of the formula



15 33. The composition of matter of Claim 30, wherein  $V^1$  is an Fc domain.

34. The composition of matter of Claim 30 wherein  $V^1$  is an IgG Fc domain.

35. The composition of matter of Claim 30 wherein  $V^1$  is an IgG1 Fc domain.

20 36. The composition of matter of Claim 30 wherein  $V^1$  comprises the sequence of SEQ ID NO: 2.

37. The composition of matter of Claim 30 wherein one or more of  $P^1$ ,  $P^2$ ,  $P^3$ , and  $P^4$  each independently comprises a sequence selected from:

$a^1a^2a^3CDa^6La^8a^9a^{10}Ca^{12}a^{13}a^{14}$  (SEQ. ID. NO: 100)

$b^1b^2b^3Cb^5b^6Db^8Lb^{10}b^{11}b^{12}b^{13}b^{14}Cb^{16}b^{17}b^{18}$  (SEQ. ID. NO: 104)

25  $c^1c^2c^3Cc^5Dc^7Lc^9c^{10}c^{11}c^{12}c^{13}c^{14}Cc^{16}c^{17}c^{18}$  (SEQ. ID. NO: 105)

$d^1d^2d^3Cd^5d^6d^7WDd^{10}Ld^{13}d^{14}d^{15}Cd^{16}d^{17}d^{18}$  (SEQ. ID. NO: 106)

$e^1e^2e^3Ce^5e^6e^7De^9Le^{11}Ke^{13}Ce^{15}e^{16}e^{17}e^{18}$  (SEQ. ID. NO: 107)

$f^1f^2f^3Kf^5Df^7Lf^9f^{10}Qf^{12}f^{13}f^{14}$  (SEQ. ID. NO: 109)

$g^1g^2g^3Cg^5PFg^8Wg^{10}Cg^{11}g^{12}g^{13}$  (SEQ ID NO: 101),  
 $h^1h^2h^3CWh^6h^7Wgh^{10}Ch^{12}h^{13}h^{14}$  (SEQ ID NO: 102), and  
 $i^{1,2,3}Ci^{5,6,7,8,9,10}Ci^{12,13,14}$  (SEQ ID NO: 103)

wherein:

- 5         $a^1, a^2, a^3$  are each independently absent or amino acid residues;  
           $a^6$  is an amino acid residue;  
           $a^9$  is a basic or hydrophobic residue;  
           $a^8$  is threonyl or isoleucyl;  
           $a^{12}$  is a neutral polar residue;  
 10        $a^{13}$  and  $a^{14}$  are each independently absent or amino acid residues;  
           $b^1$  and  $b^2$  are each independently absent or amino acid residues;  
           $b^3$  is an acidic or amide residue;  
           $b^5$  is an amino acid residue;  
           $b^6$  is an aromatic residue;  
 15        $b^8$  is an amino acid residue;  
           $b^{10}$  is T or I;  
           $b^{11}$  is a basic residue;  
           $b^{12}$  and  $b^{13}$  are each independently amino acid residues;  
           $b^{14}$  is a neutral polar residue;  
 20        $b^{16}, b^{17}$ , and  $b^{18}$  are each independently absent or amino acid  
          residues;  
           $c^1, c^2$ , and  $c^3$  are each independently absent or amino acid residues;  
           $c^5$  is an amino acid residue;  
           $c^7$  is an amino acid residue;  
 25        $c^9$  is T or I;  
           $c^{10}$  is a basic residue;  
           $c^{11}$  and  $c^{12}$  are each independently amino acid residues;  
           $c^{13}$  is a neutral polar residue;  
           $c^{14}$  is an amino acid residue;  
 30        $c^{16}$  is an amino acid residue;

- $c^{17}$  is a neutral polar residue; and  
 $c^{18}$  is an amino acid residue or is absent;  
 $d^1, d^2$ , and  $d^3$  are each independently absent or amino acid residues;  
 $d^5, d^6$ , and  $d^7$  are each independently amino acid residues;  
5  $d^{10}$  is an amino acid residue;  
 $d^{12}$  is T or I;  
 $d^{13}$  is an amino acid residue; and  
 $d^{15}, d^{16}$ , and  $d^{17}$  are each independently absent or amino acid residues;  
10  $e^1, e^2$ , and  $e^3$  are each independently absent or amino acid residues;  
 $e^5, e^6, e^7, e^9$ , and  $e^{13}$  are each independently amino acid residues;  
 $e^{11}$  is T or I; and  
 $e^{15}, e^{16}$ , and  $e^{17}$  are each independently absent or amino acid residues;  
 $f^1, f^2$ , and  $f^3$  are absent or are amino acid residues;  
15  $f^5$  is W, Y, or F;  
 $f^7$  is an amino acid residue;  
 $f^9$  is T or I;  
 $f^{10}$  is K, R, or H;  
 $f^{12}$  is C, a neutral polar residue, or a basic residue;  
20  $f^{13}$  is C, a neutral polar residue or is absent; and  
 $f^{14}$  is any amino acid residue or is absent;  
provided that only one of  $f^1, f^2$ , and  $f^3$  may be C, and only one of  $f^{12}, f^{13}$ , and  $f^{14}$  may be C;  
 $g^1, g^2$  and  $g^3$  are each independently absent or amino acid residues;  
25  $g^5$  is a neutral polar residue;  
 $g^8$  is a neutral polar residue;  
 $g^{10}$  is an acidic residue;  
 $g^{12}$  and  $g^{13}$  are each independently amino acid residues; and  
 $g^{14}$  is absent or is an amino acid residue;  
30  $h^1, h^2$ , and  $h^3$  are each independently absent or amino acid residues;



- h<sup>6</sup> is a hydrophobic residue;  
 h<sup>7</sup> is a hydrophobic residue;  
 h<sup>10</sup> is an acidic or polar hydrophobic residue; and  
 h<sup>12</sup>, h<sup>13</sup>, and h<sup>14</sup> are each independently absent or amino acid residues;  
 5 i<sup>1</sup> is absent or is an amino acid residue;  
 i<sup>2</sup> is a neutral polar residue;  
 i<sup>3</sup> is an amino acid residue;  
 i<sup>5</sup>, i<sup>6</sup>, i<sup>7</sup>, and i<sup>8</sup> are each independently amino acid residues;  
 i<sup>9</sup> is an acidic residue;  
 10 i<sup>10</sup> is an amino acid residue;  
 i<sup>12</sup> and i<sup>13</sup> are each independently amino acid residues; and  
 i<sup>14</sup> is a neutral polar residue.

38. The composition of matter of claim 37, wherein:

- a<sup>9</sup> is a basic residue.  
 15 b<sup>3</sup> is D, Q, or E;  
 b<sup>6</sup> is W or Y;  
 b<sup>11</sup> is K or R; and  
 b<sup>14</sup> is V or L.  
 c<sup>10</sup> is K or R;  
 20 c<sup>13</sup> is a I, L, or V;  
 c<sup>17</sup> is A or L;  
 f<sup>5</sup> is W;  
 f<sup>7</sup> is L; f<sup>7</sup> is K; and  
 f<sup>10</sup> is V.

- 25 39. The composition of matter of Claim 37, wherein one or more of P<sup>1</sup>, P<sup>2</sup>,  
 P<sup>3</sup>, and P<sup>4</sup> each independently comprises

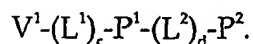
$$f^1 f^2 f^3 K W D f^7 L f^9 K Q f^{12} f^{13} f^{14}$$

(SEQ ID NO: 125).

40. The composition of matter of Claim 39 of the formula

- 30 P<sup>1</sup>-(L<sup>1</sup>)<sub>c</sub>-P<sup>2</sup>-(L<sup>2</sup>)<sub>d</sub>-V<sup>1</sup>.

41. The composition of matter of Claim 39 of the formula



42. The composition of matter of Claim 39 having an amino acid sequence selected from SEQ ID NOS: 122, 123, and 124.

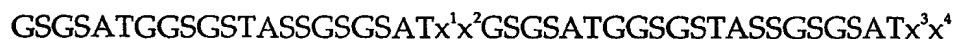
5 43. The composition of matter of Claim 40 wherein  $L^2$  is greater than 5 amino acids.

44. The composition of matter of Claim 43 wherein  $L^2$  is selected from



(SEQ ID NO: 193)

10 and



(SEQ ID NO: 194)

wherein  $x^1$  and  $x^3$  are each independently basic or hydrophobic residues and  $x^2$  and  $x^4$  are each independently hydrophobic residues.

15 45. The composition of matter of Claim 41 wherein  $L^2$  is selected from



(SEQ ID NO: 59),



(SEQ ID NO: 190)

20  $\text{GSGSATGGSGSTASSGSGSATGS}$

(SEQ ID NO: 191), and



(SEQ ID NO: 192).

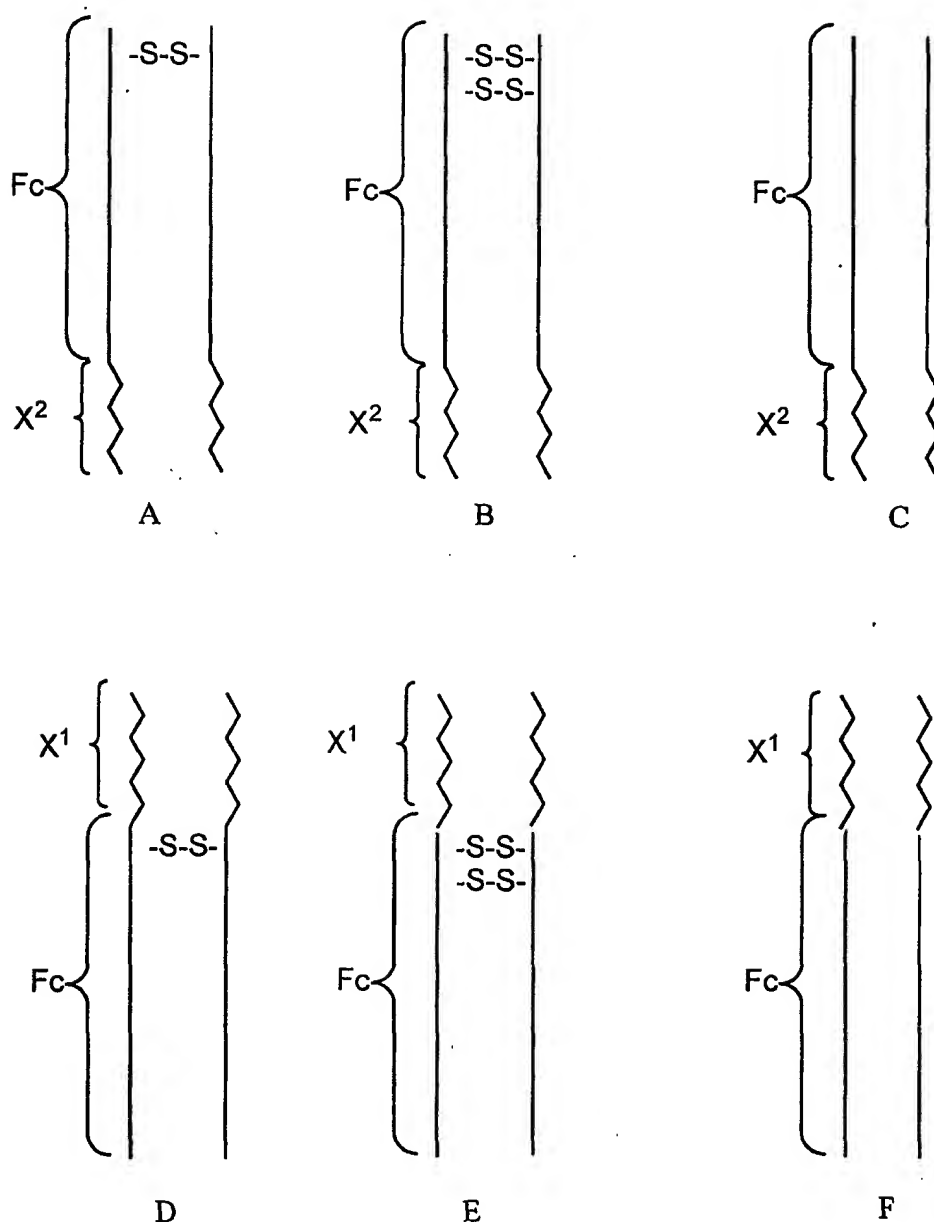
46. The composition of matter of Claim 28 comprising a sequence selected  
25 from Table 2 (SEQ ID NOS: 29-39, 60-70, and 126-188).

47. The composition of matter of Claim 30 comprising a sequence selected from Table 4 (SEQ ID NOS: 44-55).

48. The composition of matter of Claim 46, wherein  $V^1$  is an Fc domain.

49. The composition of matter of Claim 46, wherein  $V^1$  is an IgG Fc  
30 domain.

50. The composition of matter of Claim 46, wherein V<sup>1</sup> is an IgG1 Fc domain.
51. A DNA encoding a composition of matter of Claim 34.
52. An expression vector comprising the DNA of Claim 51.
- 5 53. A host cell comprising the expression vector of Claim 52.
54. The cell of Claim 53, wherein the cell is an E. coli cell.
55. A method of treating a B-cell mediated autoimmune disease, which comprises administering a composition of matter of Claim 1.
56. A method of treating a B-cell mediated autoimmune disease, which  
10 comprises administering a composition of matter of Claim 13.
57. A method of treating lupus, which comprises administering a composition of matter of Claim 1.
58. A method of treating lupus, which comprises administering a composition of matter of Claim 13.
- 15 59. A method of treating a B-cell mediated cancer, which comprises administering a composition of matter of Claim 1.
60. A method of treating a B-cell mediated cancer, which comprises administering a composition of matter of Claim 13.
61. A method of treating B-cell lymphoma, which comprises administering  
20 a composition of matter of Claim 1.
62. A method of treating B-cell lymphoma, which comprises administering a composition of matter of Claim 13.

**FIG. 1**

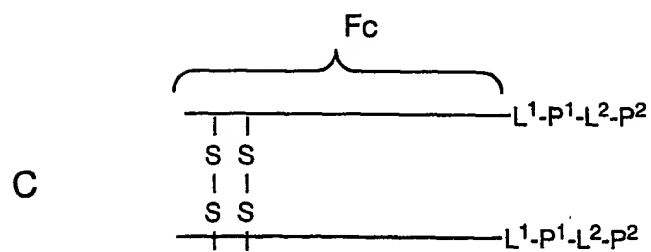
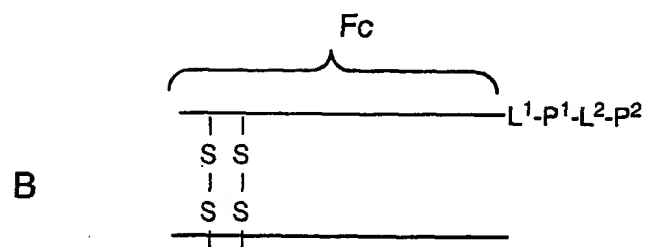
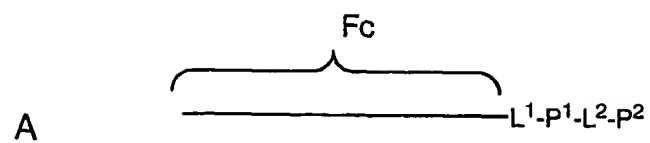
**FIG. 2**

FIG. 3

ATGGACAAAAC TCACACATGTCCACCTTGTCCAGCTCCGGAAC TCCTGGGGGGACCGTCA  
1 -----+-----+-----+-----+-----+ 60  
TACCTGTTTTGAGTGTGTACAGGTGGAACAGGTCGAGGCCTTGAGGACCCCCCTGGCAGT  
a M D K T H T C P P C P A P E L L G G P S -  
GTCTTCCTCTTCCCCCAAACCAAGGACACCCCTCATGATCTCCCGGACCCCTGAGGTC  
61 -----+-----+-----+-----+-----+ 120  
CAGAAGGAGAAGGGGGGTTTGGGTTCCTGTGGGAGTACTAGAGGCCTGGGGACTCCAG  
a V F L F P P K P K D T L M I S R T P E V -  
ACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTG  
121 -----+-----+-----+-----+-----+ 180  
TGTACGCACCACCACCTGCACTCGGTGCTTCTGGGACTCCAGTTCAAGTTGACCATGCAC  
a T C V V V D V S H E D P E V K F N W Y V -  
GACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCAGC  
181 -----+-----+-----+-----+-----+ 240  
CTGCCGCACCTCCACGTATTACGGTTCTGTTTCGGCGCCCTCCTCGTCATGTTGTCGTGC  
a D G V E V H N A K T K P R E E Q Y N S T -  
TACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTAC  
241 -----+-----+-----+-----+-----+ 300  
ATGGCACACCAGTCGCAGGAGTGGCAGGACGTGGTCCTGACCGACTTACCGTTCCCTCATG  
a Y R V V S V L T V L H Q D W L N G K E Y -  
AAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAGCC  
301 -----+-----+-----+-----+-----+ 360  
TTCACGTTCCAGAGGTTGTTTCGGGAGGGTCGGGGGTAGCTCTTTTGGTAGAGGTTTCGG  
a K C K V S N K A L P A P I E K T I S K A -  
AAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACC  
361 -----+-----+-----+-----+-----+ 420  
TTTCCCGTCGGGGCTCTTGGTGTCCACATGTGGGACGGGGGTAGGGCCCTACTCGACTGG  
a K G Q P R E P Q V Y T L P P S R D E L T -  
AAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTG  
421 -----+-----+-----+-----+-----+ 480  
TTCTTGGTCCAGTCGGACTGGACGGACAGTTTCCGAAGATAGGGTCGCTGTAGCGGCAC  
a K N Q V S L T C L V K G F Y P S D I A V -  
GAGTGGGAGAGCAATGGGAGCCGGAGAACAAC TACAAGACCACGCCCTCCCGTGTGAGC  
481 -----+-----+-----+-----+-----+ 540  
CTCACCCCTCTCGTTACCCGTCGGCCTCTTGTGATGTTCTGGTGGGAGGGCACGACCTG  
a E W E S N G Q P E N N Y K T T P P V L D -  
TCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAG  
541 -----+-----+-----+-----+-----+ 600  
AGGCTGCCGAGGAAGAAGGAGATGTCGTTTCGAGTGGCACCTGTTCTCGTCCACCGTCGTC  
a S D G S F F L Y S K L T V D K S R W Q Q -  
GGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAG  
601 -----+-----+-----+-----+-----+ 660  
CCCTTGCAGAAGAGTACGAGGCACTACGTACTCCGAGACGTGTGGTGTGATGTGCGTCTTC  
a G N V F S C S V M H E A L H N H Y T Q K -  
AGCCTCTCCCTGTCTCCGGGTAAA  
661 -----+-----+-----+-----+ 684  
TCGGAGAGGGACAGAGGCCCATTT  
a S L S L S P G K

## FIG. 4A

## 1) AGP3-8-1-a

NdeI

|

TATGCCCGGTACTTGTTCCTCCGTTCCCGTGGGAATGCACTCACGCTGGTGGAGGCGGT

1 -----+-----+-----+-----+-----+-----+ 60

GGCCCATGAACAAAGGGCAAGGGCACCCCTTACGTGAGTGCACCACCTCCGCCA

a M P G T C F P F P W E C T H A G G G G -

Sali

|

GGGG

61 ----- 69

CCCCAGCT

a G V D -

## 2) AGP3-8-2-a

NdeI

|

TATGTGGGGTGCTTGTGGCCGTTCCCGTGGGAATGTTTCAAAGAAGGTGGAGGCGGT

1 -----+-----+-----+-----+-----+-----+ 60

ACACCCACGAACAACCGGCAAGGGCACCCCTTACAAAGTTTCTTCCACCTCCGCCA

a M W G A C W P F P W E C F K E G G G G -

Sali

|

GGGG

61 ----- 69

CCCCAGCT

a G V D -

## FIG. 4B

3) AGP3-8-4-a

NdeI  
|  
TATGGTTCCGTTCTGTGACCTGCTGACTAAACACTGTTTCGAAGCTGGTGGAGGCGGT  
1 -----+-----+-----+-----+-----+-----+ 60  
ACCAAGGCAAGACACTGGACGACTGATTTGTGACAAAGCTTCGACCACCTCCGCCA  
a M V P F C D L L T K H C F E A G G G G -

Sali  
|  
GGGG  
61 ----- 69  
CCCCAGCT  
a G V D -

4) AGP3-12-4-a

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NdeI  
|  
TATGGGTTCTCGTTGTAAATACAAATGGGACGTTCTGACTAAACAGTGTTCACCAC  
1 -----+-----+-----+-----+-----+-----+ 60  
ACCCAAGAGCAACATTTATGTTTACCCTGCAAGACTGATTTGTCACAAAGGTGGTG  
a M G S R C K Y K W D V L T K Q C F H H -  
Sali  
|  
GGTGGAGGCGGTGGGG  
61 -----+-----+-----+ 81  
CCACCTCCGCCACCCAGCT  
a G G G G G V D -



FIG. 4C

## 5) AGP3-12-3-a

NdeI

|

TATGCTGCCGGGTTGTAAATGGGACCTGCTGATCAAACAGTGGGTTTGTGACCCGCTG

1 -----+-----+-----+-----+-----+-----+ 60

ACGACGGCCCAACATTTACCCTGGACGACTAGTTTGTACCCAAACACTGGGCGAC

a           M   L   P   G   C   K   W   D   L   L   I   K   Q   W   V   C   D   P   L   -

Sali

|

GGTGGAGGCGGTGGGG

61 -----+-----+ 81

CCACCTCCGCCACCCAGCT

a           G   G   G   G   G   V   D   -

## 6) AGP3-12-5-a

NdeI

|

TATGTCTGCTGACTGTTACTTCGACATCCTGACTAAATCTGACGTTTGTACTTCTTCT

1 -----+-----+-----+-----+-----+ 60

ACAGACGACTGACAATGAAGCTGTAGGACTGATTTAGACTGCAAACATGAAGAAGA

a           M   S   A   D   C   Y   F   D   I   L   T   K   S   D   V   C   T   S   S   -

Sali

|

GGTGGAGGCGGTGGGG

61 -----+-----+ 81

CCACCTCCGCCACCCAGCT

a           G   G   G   G   G   V   D   -

## FIG. 4D

## 7) AGP3-12-8-a

NdeI

|

TATGTCTGACGACTGTATGTACGACCAGCTGACTCGTATGTTTCATCTGTTCTAACCTG

1 -----+-----+-----+-----+-----+-----+ 60

ACAGACTGCTGACATACATGCTGGTCGACTGAGCATACAAGTAGACAAGATTGGAC

a M S D D C M Y D Q L T R M F I C S N L -

SalI

|

GGTGGAGGCGGTGGGG

61 -----+-----+ 81

CCACCTCCGCCACCCCAGCT

a G G G G G V D -

## 8) AGP3-12-9-a

NdeI

|

TATGGACCTGAACTGTAAATACGACGAACTGACTTACAAAGAATGGTGTCAAGTTCAAC

1 -----+-----+-----+-----+-----+-----+ 60

ACCTGGACTTGACATTTATGCTGCTTGACTGAATGTTTCTTACCACAGTCAAGTTG

a M D L N C K Y D E L T Y K E W C Q F N -

SalI

|

GGTGGAGGCGGTGGGG

61 -----+-----+ 81

CCACCTCCGCCACCCCAGCT

a G G G G G V D -

FIG. 4E

## 9) AGP3-12-10-a

NdeI

|

TATGTTCCACGACTGTAAATACGACCTGCTGACTCGTCAGATGGTTTGTCACGGTCTG

1 -----+-----+-----+-----+-----+-----+ 60

ACAAGGTGCTGACATTTATGCTGGACGACTGAGCAGTCTACCAAACAGTGCCAGAC

a M F H D C K Y D L L T R Q M V C H G L -

Sali

|

GGTGGAGGCGGTGGGG

61 -----+-----+ 81

CCACCTCCGCCACCCAGCT -

a G G G G G V D -

## 10) AGP3-12-11-a

NdeI

|

TATGCGTAACCACTGTTTCTGGGACCACCTGCTGAAACAGGACATCTGTCCGTCTCCG

1 -----+-----+-----+-----+-----+ 60

ACGCATTGGTGACAAAGACCCTGGTGGACGACTTTGTCCTGTAGACAGGCAGAGGC

a M R N H C F W D H L L K Q D I C P S P -

Sali

|

GGTGGAGGCGGTGGGG

61 -----+-----+ 81

CCACCTCCGCCACCCAGCT

a G G G G G V D -

FIG. 4F

## 11) AGP3-12-14-a

|  
NdeI  
|  
TATGGCTAACCAGTGTGGTGGGACTCTCTGCTGAAAAAAAAACGTTGTGAATTCTTC  
1 -----+-----+-----+-----+-----+ 60  
ACCGATTGGTCACAACCACCCTGAGAGACGACTTTTTTTTGCAAACACTTAAGAAG  
a M A N Q C W W D S L L K K N V C E F F -  
SalI  
|  
GGTGGAGGCGGTGGGG  
61 -----+-----+-----+-----+ 81  
CCACCTCCGCCACCCAGCT  
a G G G G G V D -

## 12) AGP3 Consensus

NdeI  
|  
TATGTTCCACGACTGCAAATGGGACCTGCTGACCAAACAGTGGGTTTGCCACGGTCTG  
1 -----+-----+-----+-----+-----+ 60  
gtATACAAGGTGCTGACGTTTACCCTGGACGACTGGTTTGTACCCAAACGGTGCCAGAC  
a M F H D C K W D L L T K Q W V C H G L -  
SalI  
|  
GGTGGAGGCGGTGGGG  
61 -----+-----+-----+-----+ 81  
CCACCTCCGCCACCCAGCT  
a G G G G G V D -

P  
f  
l  
l  
l  
0  
8  
I

1  
GATCAGCAGTCCCCGGAACATCGTAGCTGACGCCCTTCGCGTTGCTCAGTTGTGCCAACCCC  
CTAGTCGTCAGGGGCCTTGTAGCATCGACTGCGGAAGCGCAACGAGTCAACAGGTTGGGG  
61  
GGAAACGGGAAAAAGCAAGTTTTCCCCGCTCCCGGCGTTTCAATAACTGAAACCATACT  
CCTTTGCCCTTTTTCGTTCAAAAGGGGCGAGGGCCGCAAAGTTATTGACTTTTGGTATGA  
121  
ATTTACAGTTTAAATCACATTAAACGACAGTAATCCCCGTTGATTTGTGCGCCAACACA  
TAAAGTGTCAAATTAGTGTAATTTGCTGTCTATTAGGGGCAACTAAACACGCGTTGTGT  
181  
CTAGCTTCGTACAAATTCCTCAAGTCGCTGATTTCAAAAACTGTAGTATCCTCTGCGAAAC  
CTAGAAGCAGTGTTAAGAGTTTCAGCGACTAAAGTTTTTTGACATCATAGGAGACGCTTTG  
241  
GATCCCTGTTTGAGTATTGAGGAGGCGAGATGTCGCAGACAGAAAATGCAGTGACTTCCT  
CTAGGGACAACTCATAACTCCTCCGCTCTACAGCGTCTGTCTTTTACGTCACTGAAGGA  
301  
CATTGAGTCAAAAGCGGTTTGTGCGCAGAGGTAAGCCTATGACTGACTCTGAGAAAACAAA  
GTAAGTCAAGTTTTCGCCAAACACGCGTCTCCATTCCGATACTGACTGAGACTCTTTGTTT  
361  
TGGCCGTTGTTGCAAGAAAACGTCTTACACACAAAAGAGATAAAAAGTTTTTGTCAAAAATC  
ACCGGCAACAACGTTCTTTTGCAGAATGTGTGTTTCTCTATTTTCAAAAACAGTTTTTAG  
421  
CTCTGAAGGATCTCATGGTTGAGTACTGCGAGAGAGAGGGGATAACACAGGCTCAGTTTCG  
GAGACTTCCTAGAGTACCAACTCATGACGCTCTCTCTCCCTATTGTGTCCGAGTCAAGC  
480  
L K D L M V E Y C E R E G I T Q A Q F V -

FIG. 5B

```

                                     -35
                                     -----
                               ---- Promoter (PrepA) ---->
                                     |-- copB binding site --|
481 TTGAGAAAATCATCAAAGATGAACTGCAAAGACTGGATATACTAAAGTAAAGACTTTACT
-----+-----+-----+-----+-----+-----+-----+
541 AACTCTTTTAGTAGTTTCTACTTGACGTTTCTGACCTATATGATTTTCATTTCTGAAATGA
      E K I I K D E L Q R L D I L K *

                                     -10
                                     -----
541 TTGTGGCGTAGCATGCTAGATTACTGATCGTTTAAGGAATTTTGTGGCTGGCCACGCCCGT
-----+-----+-----+-----+-----+-----+-----+
600 AACACCGCATCGTACGATCTAATGACTAGCAAATTCCTTAAACACCGACCGGTGCGGCA
      |-- mRNA -->

      D
      B r
      m d
      n I
      I I
      |<-----
601 AAGGTGGCAAGGAAGTGGTTCTGATGTGGATTTACAGGAGCCAGAAAAGCAAAAACCCCG
-----+-----+-----+-----+-----+-----+-----+
660 TTCCACCGTTCCTTGACCAAGACTACACCTAAATGTCTCGGTCTTTTCGTTTTTGGGGC
      M W I Y R S Q K S K N P D -
      --- copT (ORF) --->

<----- copA RNAI -----
661 ATAATCTTCTTCAACTTTTGCGAGTACGAAAAGATTACCGGGGCCCACTTAAACCGTATA
-----+-----+-----+-----+-----+-----+-----+
720 TATTAGAAGAAGTTGAAAACGCTCATGCTTTTCTAATGGCCCCGGGTGAATTTGGCATAT
      N L L Q L L R V R K D Y R G P L K P Y S -

<----- Promoter (RNAI) -----
                                     -10          -35
<-----+-----+-----+-----+-----+-----+-----+
721 GCCAACAATTCAGCTATGCGGGGAGTATAGTTATATGCCCGGAAAAGTTCAAGACTTCTT
-----+-----+-----+-----+-----+-----+-----+
780 CGGTTGTTAAGTCGATACGCCCCCTCATATCAATATACGGGCCTTTTCAAGTTCTGAAGAA
      Q Q F S Y A G S I V I C P E K F K T S F -

781 TCTGTGCTCGCTCCTTCTGCGCATTGTAAGTGCAGGATGGTGTGACTGATCTTCACCAA
-----+-----+-----+-----+-----+-----+-----+
840 AGACACGAGCGAGGAAGACGCGTAACATTACGTCCTACCACACTGACTAGAAGTGTTT
      C A R S F C A L *          M T D L H Q T -
      --- repA1 protein --->

      D
      r
      a
      i
      i
      I
      I
841 CGTATTACCGCCAGGTAAAGAACCCGAATCCGGTGTTTACACCCCGTGAAGGTGCAGGAA
-----+-----+-----+-----+-----+-----+-----+
900 GCATAATGGCGGTCCATTTCTTGGGCTTAGGCCACAAATGTGGGGCACTTCCACGTCCTT
      Y Y R Q V K N P N P V F T P R E G A G T -

901 CGCTGAAGTTCTGCGAAAACTGATGAAAAGGCGGTGGGCTTCACTTCCCGTTTGTATT
-----+-----+-----+-----+-----+-----+-----+
960 GCGACTTCAAGACGCTTTTGTACTACCTTTTCCGCCACCCGAAGTGAAGGGCAAACTAA
      L K F C E K L M E K A V G F T S R F D F -

```

12/37

FIG. 5C

B  
s  
t  
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I

961 TCGCCATTTCATGTGGCGCACGCCCCGTTTCGCGTGATCTGCGTCGCCGTATGCCACCAGTGC  
-----+-----+-----+-----+-----+-----+-----+-----+-----+ 1020  
AGCGGTAAGTACACCGCGTGCAGGCAAGCGCACTAGACGCAGCGGCATACGGTGGTCACG  
c A I H V A H A R S R D L R R R M P P V L -

1021 TGCCTCGTCGGGCTATTGATGCGCTCTTGACAGGGCTGTGTTTCCACTATGACCCGCTGG  
-----+-----+-----+-----+-----+-----+-----+-----+-----+ 1080  
ACGCAGCAGCCCGATAACTACGCGAGAAGCTCCCGACACAAAGGTGATACTGGGCGACC  
c R R R A I D A L L Q G L C F H Y D P L A -

1081 CCAACCGCGTCCAGTGCTCCATCACCACGCTGGCCATTGAGTGCGGACTGGCGACGGAGT  
-----+-----+-----+-----+-----+-----+-----+-----+-----+ 1140  
GGTTGGCGCAGGTCACGAGGTAGTGGTGCGACCGGTAACCTACGCCTGACCGCTGCCTCA  
c N R V Q C S I T T L A I E C G L A T E S -

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e  
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I

1141 CTGCTGCCGGAAGAACTCTCCATCACCCGTGCCACCCGTGCCCTGACGTTCTGTGACAGC  
-----+-----+-----+-----+-----+-----+-----+-----+-----+ 1200  
GACGACGGCCTTTTGAGAGGTAGTGGGCACGGTGGGCACGGGACTGCAAGGACAGTCTCG  
c A A G K L S I T R A T R A L T F L S . E L -

1201 TGGGACTGATTACCTACCAGACGGAATATGACCCGCTTATCGGGTGCTACATTCCGACCG  
-----+-----+-----+-----+-----+-----+-----+-----+-----+ 1260  
ACCCTGACTAATGGATGGTCTGCCTTATACTGGGCGAATAGCCCACGATGTAAGGCTGGC  
c G L I T Y Q T E Y D P L I G C Y I P T D -

1261 ATATCACGTTTACATCTGCACTGTTTGTGTCCTCGATGTATCAGAGGAGGCAGTGGCCG  
-----+-----+-----+-----+-----+-----+-----+-----+-----+ 1320  
TATAGTGCAAGTGTAGACGTGACAAACGACGGGAGCTACATAGTCTCCTCCGTACCCGGC  
c I T F T S A L F A A L D V S E E A V A A -

1321 CCGCGCGCCGACCCGTGTGGTATGGGAAAACAAACAACGCAAAAAGCAGGGGCTGGATA  
-----+-----+-----+-----+-----+-----+-----+-----+-----+ 1380  
GGCGCGCGGCGTCGGCACACCATAACCCCTTTGTTTGTGCGTTTTTCGTCCCCGACCTAT  
c A R R S R V V W E N K Q R K K Q G L D T -

1381 CCCTGGGCATGGATGAACTGATAGCGAAAGCCTGGCGTTTTGTTCGTGAGCGTTTTTCGCA  
-----+-----+-----+-----+-----+-----+-----+-----+-----+ 1440  
GGGACCCGTACCTACTTGACTATCGCTTTCGGACCGCAAAACAAGCACTCGCAAAAAGCGT  
c L G M D E L I A K A W R F V R E R F R S -

A  
f  
l  
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I

1441 GTTATCAGACAGAGCTTAAGTCCCGTGGAATAAAGCGTGCCCGTGCGCGTCGTGATGCGG  
-----+-----+-----+-----+-----+-----+-----+-----+-----+ 1500  
CAATAGTCTGTCTCGAATTCAGGGCACCTTATTTTCGCACGGGCACGCGCAGCACTACGCC  
c Y Q T E L K S R G I K R A R A R R D A D -

FIG. 5D

1501 ACAGGGAACGTCAGGATATTGTCACCCTGGTGAAACGGCAGCTGACGCGCGAAATCGCGG  
-----+-----+-----+-----+-----+ 1560  
c TGTCCCTTGCAGTCCTATAACAGTGGGACCACTTTGCCGTCGACTGCGCGCTTTAGCGCC  
R E R Q D I V T L V K R Q L T R E I A E -

1561 AAGGGCGCTTCACTGCCAATCGTGAGGCGGTAAAACGCGAAGTTGAGCGTCGTGTGAAGG  
-----+-----+-----+-----+-----+ 1620  
c TTCCCGCGAAGTGACGGTTAGCACTCCGCCATTTTGCGCTTCAACTCGCAGCACACTTCC  
G R F T A N R E A V K R E V E R R V K E -

1621 AGCGCATGATTCTGTACGTAACCGTAATTACAGCCGGCTGGCCACAGCTTCCCCCTGAA  
-----+-----+-----+-----+-----+ 1680  
c TCGCGTACTAAGACAGTGCATTGGCATTAAATGTCGGCCGACCGGTGTCGAAGGGGGACTT  
R M I L S R N R N Y S R L A T A S P \*

1681 AGTGACCTCCTCTGAATAATCCGGCCTGCGCCGGAGGCTTCCGCACGTCTGAAGCCCGAC  
-----+-----+-----+-----+-----+ 1740  
TCACTGGAGGAGACTTATTAGCCGGACGCGGCCTCCGAAGGCGTGCAGACTTCCGGGCTG

P  
f  
l  
M  
I

1741 AGCGCACAAAAATCAGCACCACATACAAAAACAACCTCATCATCCAGCTTCTGGTGCA  
-----+-----+-----+-----+-----+ 1800  
TCGCGTGTTTTTTAGTCGTGGTGTATGTTTTTTGTTGGAGTAGTAGGTCGAAGACCACGT

1801 TCCGGCCCCCCTGTTTTCGATACAAAACACGCCTCACAGACGGGGAATTTTGCTTATCC  
-----+-----+-----+-----+-----+ 1860  
AGGCCGGGGGGGACAAAAGCTATGTTTTGTGCGGAGTGTCTGCCCTTAAACGAATAGG

|----- ori -----  
1861 ACATTAACTGCAAGGGACTTCCCCATAAGGTTACAACCGTTCATGTCATAAAGCGCCAT  
-----+-----+-----+-----+-----+ 1920  
TGTAATTTGACGTTCCCTGAAGGGGTATTCCAATGTTGGCAAGTACAGTATTTTCGCGGTA

----- ori -----  
1921 CCGCCAGCGTTACAGGGTGCAATGTATCTTTTAAACACCTGTTTATATCTCCTTTAACT  
-----+-----+-----+-----+-----+ 1980  
GGCGGTGCAATGTCCACGTTACATAGAAAATTTGTGGACAAATATAGAGGAAATTTGA

----- | -----  
1981 ACTTAATTACATTCATTTAAAAAGAAAACCTATTCACTGCCTGTCCTTGGACAGACAGAT  
-----+-----+-----+-----+-----+ 2040  
TGAATTAATGTAAGTAAATTTTCTTTTGGATAAGTGACGGACAGGAACCTGTCTGTCTA

2041 ATGCACCTCCCACCGCAAGCGGGGGGCCCTACCGGAGCCGCTTTAGTTACAACACTCAG  
-----+-----+-----+-----+-----+ 2100  
a TACGTGGAGGGTGGCGTTCCGCCCGCGGGGATGGCCTCGGCGAAATCAATGTTGTGAGTC  
M H L P P Q A A G P Y R S R F S Y N T Q -  
--- repA4 protein ---> |----->

2101 ACACAACCACCAGAAAAACCCCGGTCCAGCGCAGAACTGAAACCACAAAGCCCCCTCCCTC  
-----+-----+-----+-----+-----+ 2160  
a TGTGTTGGTGGTCTTTTTGGGGCCAGGTCGCGTCTTGACTTTGGTGTTCGGGGAGGGAG  
T Q P P E K P R S S A E L K P Q S P S L -

2161 ATAAC TGAAAAGCGCCCCGCCCGGTCCGAAGGGCCGGAACAGAGTCGCTTTTAATTAT  
-----+-----+-----+-----+-----+ 2220  
a TATTGACTTTTCGCCGGGGCGGGGCCAGGCTTCCCGGCCTTGTCCTCAGCGAAAATTAATA  
I T E K R P R P G P K G R N R V A F N Y -



FIG. 5E

2221 GAATGTTGTAAC TACTTCATCATCGCTGTCAGTCTTCTCGCTGGAAGTTCTCAGTACACG 2280  
-----+-----+-----+-----+-----+-----+-----+  
a CTTACAACATTGATGAAGTAGTAGCGACAGTCAGAAGAGCGACCTTCAAGAGTCATGTGC  
E C C N Y F I I A V S L L A G S S Q Y T -

BS  
gf  
li  
II  
/  
2281 CTCGTAAGCGGCCCTGACGGCCCGCTAACGCGGAGATACGCCCCGACTTCGGGTAAACCC 2340  
-----+-----+-----+-----+-----+-----+-----+  
a GAGCATTGCGCCGGGACTGCCGGGCGATTGCGCCTCTATGCGGGGCTGAAGCCCATTTGGG  
L V S G P D G P L T R R Y A P T S G K P -

2341 TCGTCGGGACCACTCCGACCGCGCACAGAAGCTCTCTCATGGCTGAAAGCGGGTATGGTC 2400  
-----+-----+-----+-----+-----+-----+-----+  
a AGCAGCCCTGGTGAGGCTGGCGCGTGTCTTCGAGAGAGTACCGACTTTCGCCCATAACCAG  
S S G P L R P R T E A L S W L K A G M V -

2401 TGGCAGGGCTGGGGATGGGTAAGGTGAAATCTATCAATCAGTACCGGCTTACGCCGGGCT 2460  
-----+-----+-----+-----+-----+-----+-----+  
a ACCGTCCCAGCCCTACCCATTCCACTTTAGATAGTTAGTCATGGCCGAATGCGGCCCGA  
W Q G W G W V R \*

B  
s  
t  
E  
I  
I  
2461 TCGGCGGTTTTACTCCTGTTTCATATATGAAACAACAGGTCACCGCCTTCCATGCCGCTG 2520  
-----+-----+-----+-----+-----+-----+-----+  
AGCCGCCAAAATGAGGACAAAGTATATACTTTGTTGTCCAGTGGCGGAAGGTACGGCGAC

B  
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p  
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l  
I  
2521 ATGCGGCATATCCTGGTAACGATATCTGAATTGTTATACATGTGTATATACGTGGTAATG 2580  
-----+-----+-----+-----+-----+-----+-----+  
TACGCCGTATAGGACCATGCTATAGACTTAACAATATGTACACATATATGCACCATTAC

2581 ACAAAAATAGGACAAGTTAAAAATTTACAGGCGATGCAATGATTCAAACACGTAATCAAT 2640  
-----+-----+-----+-----+-----+-----+-----+  
TGTTTTTATCCTGTTCAATTTTAAATGTCCGCTACGTTACTAAGTTTGTGCATTAGTTA

2641 ATCGGGGTGGGCGAAGAACTCCAGCATGAGATCCCCGCGCTGGAGGATCATCCAGCCGG 2700  
-----+-----+-----+-----+-----+-----+-----+  
TAGCCCCCACC CGCTTCTTGAGGTCTACTCTAGGGGCGCGACCTCCTAGTAGGTGGGCC

2701 CGTCCCGGAAAACGATTCCGAAGCCCAACCTTTTCATAGAAGGCGGCGGTGGAATCGAAAT 2760  
-----+-----+-----+-----+-----+-----+-----+  
GCAGGGCCTTTTGCTAAGGCTTCGGGTTGGAAGTATCTTCCGCCGCCACCTTAGCTTTA

FIG. 5F

|      | N<br>S<br>P<br>V  | B<br>P<br>I<br>I |
|------|---|------------------|
|      | CTCGTGATGGCAGGTTGGGCCTCGCTTGGTCGGTCATTTCGAACCCAGAGTCCCCTCA        |                  |
| 2761 | -----+-----+-----+-----+-----+-----+                              | 2820             |
|      | GAGCACTACCGTCCAACCCGCAGCGAACCAGCCAGTAAGCTTGGGGTCTCAGGGCGAGT       |                  |
|      | GAAGAACTCGTCAAGAAGGCGATAGAAGGCCGATGCGCTGCGAATCGGGAGCGGCGATAACC    |                  |
| 2821 | -----+-----+-----+-----+-----+-----+                              | 2880             |
| f    | * CTTCTTGAGCAGTTCTTCCGCTATCTTCCGCTACGCGACGCTTAGCCCTCGCCGCTATGG -  |                  |
|      | <--- APHII protein [kanamycin resistance gene] --->               |                  |
|      | GTAAAGCACGAGGAAGCGGTCAGCCCCATTGCGCCGAAGCTCTTCAGCAATATCACGGGT      |                  |
| 2881 | -----+-----+-----+-----+-----+-----+                              | 2940             |
| f    | CATTTCTGTGCTCCTTCGCCAGTTCGGGTAAAGCGGCGGTTGAGAAGTCGTTATAGTGCCCA    |                  |
|      | Y L V L F R D A W E G G L E E A I D R T -                         |                  |
|      | AGCCAACGCTATGTCCTGATAGCGGTCCGCCACACCCAGCCGGCCACAGTCGATGAATCC      |                  |
| 2941 | -----+-----+-----+-----+-----+-----+                              | 3000             |
| f    | TCGGTTGCGATACAGGACTATCGCCAGGCGGTTGTGGGTTCGGCCGGTGTCTAGCTACTTAGG - |                  |
|      | A L A I D Q Y R D A V G L R G C D I F G -                         |                  |
|      | AGAAAAGCGGCCATTTTCCACCATGATATTCGGCAAGCAGGCATCGCCATGAGTCACGAC      |                  |
| 3001 | -----+-----+-----+-----+-----+-----+                              | 3060             |
| f    | TCTTTTCGCCGGTAAAAGGTGGTACTATAAGCCGTTTCGTCCGTAGCGGTACTCAGTGCTG -   |                  |
|      | S F R G N E V M I N P L C A D G H T V V -                         |                  |
|      | GAGATCCTCGCCGTCGGGCATGCGCGCCTTGAGCCTGGCGAACAGTTCGGCTGGCGCGAG      |                  |
| 3061 | -----+-----+-----+-----+-----+-----+                              | 3120             |
| f    | CTCTAGGAGCGGCAGCCCGTACGCGCGGAAGTTCGGACCGCTTGTCAGCCGACCGCGCTC -    |                  |
|      | L D E G D P M R A K L R A F L E A P A L -                         |                  |
|      | CCCCTGATGCTCTTCGTCCAGATCATCTGATCGACAAGACCGGCTTCCATCCGAGTACG       |                  |
| 3121 | -----+-----+-----+-----+-----+-----+                              | 3180             |
| f    | GGGGACTACGAGAAGCAGGTCTAGTAGGACTAGCTGTTCTGGCCGAAGGTAGGCTCATGC -    |                  |
|      | G Q H E E D L D D Q D V L G A E M R T R -                         |                  |
|      | TGCTCGCTCGATGCGATGTTTCGCTTGGTGGTCGAATGGGCAGGTAGCCGGATCAAGCGT      |                  |
| 3181 | -----+-----+-----+-----+-----+-----+                              | 3240             |
| f    | ACGAGCGAGCTACGCTACAAAGCGAACCACAGCTTACCCGTCCATCGGCC TAGTTCGCA -    |                  |
|      | A R E I R H K A Q H D F P C T A P D L T -                         |                  |
|      | ATGCAGCCGCCGATTGTCATCAGCCATGATGGATACTTTCTCGGCAGGAGCAAGGTGAGA      |                  |
| 3241 | -----+-----+-----+-----+-----+-----+                              | 3300             |
| f    | TACGTCGGCGGCGTAACGTAGTCGGTACTACCTATGAAAGAGCCGTCCTCGTTCCTACTCT -   |                  |
|      | H L R R M A D A M I S V K E A P A L H S -                         |                  |
|      | TGACAGGAGATCCTGCCCCGGCACTTCGCCCAATAGCAGCCAGTCCCTTCCCGCTTCAGT      |                  |
| 3301 | -----+-----+-----+-----+-----+-----+                              | 3360             |
| f    | ACTGTCTCTTAGGACGGGGCGTGAAGCGGTTATCGTCGGTCAGGGAAGGGCGAAGTCA -      |                  |
|      | S L L D Q G P V E G L L L W D R G A E T -                         |                  |
|      | GACAACGTCGAGCACAGCTGCGCAAGGAACGCCCCTCGTGGCCAGCCACGATAGCCGCGC      |                  |
| 3361 | -----+-----+-----+-----+-----+-----+                              | 3420             |
| f    | CTGTTGCAGCTCGTGTGCAGCGGTTCTTTCGGGGCAGCACCAGTTCGGTGTCTATCGGCGCG -  |                  |
|      | V V D L V A A C P V G T T A L W S L R A -                         |                  |
|      | TGCCTCGTCTGCAATTCAATTCAGGACACCGGACAGGTCGGTCTTGACAAAAAGAACCGG      |                  |
| 3421 | -----+-----+-----+-----+-----+-----+                              | 3480             |
|      | ACGGAGCAGGACGTTAAGTAAGTCTGTGGCCTGTCCAGCCAGAAGTGTCTTCTTGGCC        |                  |

FIG. 5G

```

f      A E D Q L E N L V G S L D T K V F L V P -
      GCGCCCCTGCGCTGACAGCCGGAACACGGCGGCATCAGAGCAGCCGATTGTCTGTTGTGC
3481  -----+-----+-----+-----+-----+-----+-----+ 3540
      CGCGGGGACGCGACTGTCGGCCTTGTGCCGCGTAGTCTCGTCGGCTAACAGACAACACG
f      R G Q A S L R F V A A D S C G I T Q Q A -
                                     E
                                     a
                                     g
                                     I
      CCAGTCATAGCCGAATAGCCTCTCCACCCAAGCGCGGAGAACCTGCGTGCAATCCATC
3541  -----+-----+-----+-----+-----+-----+-----+ 3600
      GGTCAGTATCGGCTTATCGGAGAGGTGGGTTCCGCCGCCCTCTTGGACGCACGTTAGGTAG
f      W D Y G F L R E V W A A P S G A H L G D -
      TTGTTCAATCATGCGAAACGATCCTCATCCTGTCTCTTGATCTGATCTTGATCCCCTGCG
3601  -----+-----+-----+-----+-----+-----+-----+ 3660
      AACAAGTTAGTACGCTTTGCTAGGAGTAGGACAGAGAAGTAGACTAGAAGTAGGGGACGC
f      Q E I M
<-- APHII (kanamycin resistance) protein --)
                                     <--- mRNA APHII ---|-----
                                     -10.
3661  CCATCAGATCCTTGGCGGCAAGAAAGCCATCCAGTTTACTTTGCAGGGCTTCCCAACCTT
      -----+-----+-----+-----+-----+-----+-----+ 3720
      GGTAGTCTAGGAACCGCGTTCCTTTTCGGTAGGTCAAATGAAACGTCCCGAAGGGTTGGAA

                                     -35
                                     -----
      <----- Promoter (APHII) -----
3721  ACCAGAGGGCGCCCCAGCTGGCAATTCCGGTTCGCTTGCTGTCCATAAAACGCCCAGTC
      -----+-----+-----+-----+-----+-----+-----+ 3780
      TGGTCTCCCGCGGGGTCGACCGTTAAGGCCAAGCGAACGACAGGTATTTTGGCGGGTCAG
      TAGCTATCGCCATGTAAGCCCACTGCAAGCTACCTGCTTTCTCTTTGCGCTTGCGTTTTTC
3781  -----+-----+-----+-----+-----+-----+-----+ 3840
      ATCGATAGCGGTACATTCGGGTGACGTTTCGATGGACGAAAGAGAAACGCGAACGCAAAAG
      CCTTGTCCAGATAGCCCAGTAGCTGACATTCATCCGGGGTCAGCACCGTTTCTGCGGACT
3841  -----+-----+-----+-----+-----+-----+-----+ 3900
      GGAACAGGTCTATCGGGTCATCGACTGTAAGTAGGCCCCAGTCGTGGCAAAGACGCCTGA
      GGCTTTCTACGTGTTCGCTTCCTTTTAGCAGCCCTTGCGCCCTGAGTGCTTGCGGCAGCG
3901  -----+-----+-----+-----+-----+-----+-----+ 3960
      CCGAAAGATGCACAAGGCGAAGGAAATCGTCGGGAACGCGGGACTCACGAACGCCGTCGC

      |----- par locus -----
3961  TGAAGCTACATATATGTGATCCGGGCAAATCGCTGAATATTCCTTTTGTCTCCGACCATC
      -----+-----+-----+-----+-----+-----+-----+ 4020
      ACTTCGATGTATATACACTAGGCCCGTTTAGCGACTTATAAGGAAAACAGAGGCTGGTAG

                                     B
                                     c
                                     g
                                     I
      ----- par locus -----
4021  AGGCACCTGAGTCGCTGTCTTTTTCGTGACATTTCGTTTCGCTCAGCGCTCTGGCA
      -----+-----+-----+-----+-----+-----+-----+ 4080
      TCCGTGGACTCAGCGACAGAAAAGCACTGTAAGTCAAGCGACGCGAGTGCCGAGACCGT

      ----- par locus -----

```

FIG. 5H

```

GTGAATGGGGGTAAATGGCACTACAGGCGCCTTTTATGGATTTCATGCAAGGAACTACCC
4081 -----+-----+-----+-----+-----+-----+-----+ 4140
CACTTACCCCCATTTACCGTGATGTCCGCGGAAAATACCTAAGTACGTTCCTTTGATGGG

----- par locus -----
ATAATACAAGAAAAGCCCGTCACGGGCTTCTCAGGGCGTTTTATGGCGGGTCTGCTATGT
4141 -----+-----+-----+-----+-----+-----+-----+ 4200
TATTATGTTCTTTTCGGGCAGTGCCCGAAGAGTCCCGCAAAATACCGCCCAGACGATACA

----- par locus -----
GGTGCTATCTGACTTTTTGCTGTTTCAGCAGTTCCTGCCCTCTGATTTTCCAGTCTGACCA
4201 -----+-----+-----+-----+-----+-----+-----+ 4260
CCACGATAGACTGAAAAACGACAAGTCGTCAAGGACGGGAGACTAAAAGGTCAGACTGGT

----- par locus -----
CTTCGGATTATCCCGTGACAGGTCAATTCAGACTGGCTAATGCACCCAGTAAGGCAGCGGT
4261 -----+-----+-----+-----+-----+-----+-----+ 4320
GAAGCCTAATAGGGCACTGTCCAGTAAGTCTGACCGATTACGTGGGTTCATTCGTCGCCA

                                     N      B
                                     s      s
                                     i      a
                                     I      I
-----+-----+-----+-----+-----+-----+-----+
4321 ATCATCAACAGGCTTACCCGCTTACTGTCTGAAGACGTGCGTAACGTATGCATGGTCTCC 4380
TAGTAGTTGTCCGAATGGGCAGAATGACAGCTTCTGCACGCATTGCATACGTACCAGAGG

                                     T1 hairpin
                                     ----->-----<-----
4381 CCATGCGAGAGTAGGGAACAGCCAGGCATCAAATAAAACGAAAGGCTCAGTCGAAAGACT 4440
GGTACGCTCTCATCCCTTGACGGTCCGTAGTTTATTTTGCTTTCCGAGTCAGCTTCTGA

-----+-----+-----+-----+-----+-----+-----+
4441 GGGCCTTTTCGTTTATCTGTTGTTGTCGGTGAACGCTCTCCTGAGTAGGACAAATCCGC 4500
CCCGGAAAGCAAAATAGACAACAAACAGCCACTTGCGAGAGGACTCATCTGTTTAGGCG
-- T1 stop -->|

P
S
P
1
4
0
6
I
4501 CGGGAGCGGATTTGAACGTTGCGAAGCAACGGCCCGGAGGGTGGCGGGCAGGACGCCCGC 4560
GCCCTCGCCTAAACTTGCAACGCTTCGTTGCCGGGCCTCCCACCGCCCGTCTGCGGGCG

                                     T2 hairpin
                                     ----->-----<-----
4561 CATAAACTGCCAGGCATCAAATTAAGCAGAAGGCCATCCTGACGGATGGCCTTTTTCGCT 4620
GTATTTGACGGTCCGTAGTTTAATTCGTCTTCCGGTAGGACTGCCTACCGGAAAAACGCA
----- T2 stop ----->|

```

FIG. 5I

A  
a  
t  
I  
I

4621 TTCTACAAACTCTTTTGTATTATTTTCTAAATACATTCAAATATGGACGTCGTACTTAAC 4680  
-----+-----+-----+-----+-----+  
AAGATGTTTGAGAAAACAAATAAAAAGATTATGTAAGTTTATACCTGCAGCATGAATTG  
\* -

4681 TTTTAAAGTATGGGCAATCAATTGCTCCTGTTAAAATTGCTTTAGAAATACTTTGGCAGC 4740  
-----+-----+-----+-----+-----+  
AAAATTTTCATACCCGTTAGTTAACGAGGACAATTTTAACGAAATCTTTATGAAACCGTCG  
d \* S K F Y P C D I A G T L I A K S I S Q C -  
|<--- luxR protein ---

4741 GGTTTGTTGTATTGAGTTTCATTTGCGCATTGGTTAAATGGAAAGTGACCGTGCGCTTAC 4800  
-----+-----+-----+-----+-----+  
CCAAACAACATAACTCAAAGTAAACGCGTAACCAATTTACCTTTTCACTGGCACGCGAATG  
d R N T T N L K M Q A N T L H F T V T R K -

4801 TACAGCCTAATATTTTGAATATCCCAAGAGCTTTTTCCTTCGCATGCCCACGCTAAAC 4860  
-----+-----+-----+-----+-----+  
ATGTCGGATTATAAAAACCTTTATAGGGTTCTCGAAAAAGGAAGCGTACGGGTGCGATTTG  
d S C G L I K S I D W S S K G E C A W A L -

4861 ATTCTTTTCTCTTTTGGTTAAATCGTTGTTTGATTATTATTGCTATATTTATTTTTC 4920  
-----+-----+-----+-----+-----+  
TAAGAAAAAGAGAAAACCAATTTAGCAACAACTAAATAATAACGATATAAATAAAAAAG  
d C E K E R K T L D N N S K N N A I N I K -

4921 GATAATTATCAACTAGAGAAGGAACAATTAATGGTATGTTTCATACACGCATGTAAAAATA 4980  
-----+-----+-----+-----+-----+  
CTATTAATAGTTGATCTCTTCCTTGTTAATTACCATAACAAGTATGTGCGTACATTTTAT  
d R Y N D V L S P V I L P I N M C A H L F -

B  
S  
m  
I

4981 AACTATCTATATAGTTGTCTTTCTCTGAATGTGCAAAACTAAGCATTCCGAAGCCATTAT 5040  
-----+-----+-----+-----+-----+  
TTGATAGATATATCAACAGAAAGAGACTTACACGTTTTGATTTCGTAAGGCTTCGGTAATA  
d L S D I Y N D K E S H A F S L M G F G N -

5041 TAGCAGTATGAATAGGGAACTAAACCCAGTGATAAGACCTGATGATTTTCGCTTCTTTAA 5100  
-----+-----+-----+-----+-----+  
ATCGTCATACTTATCCCTTTGATTGGGTCACTATTCTGGACTACTAAAGCGAAGAAATT  
d N A T H I P F S F G T I L G S S K A E K -

5101 TTACATTTGGAGATTTTTTATTTACAGCATTGTTTTCAAATATATTCCAATTAATCGGTG 5160  
-----+-----+-----+-----+-----+  
AATGTAAACCTCTAAAAAATAAATGTCGTAACAAAAGTTTATATAAGGTTAATTAGCCAC  
d I V N P S K K N V A N N E F I N W N I P -

5161 AATGATTGGAGTTAGAATAATCTACTATAGGATCATATTTTATTAAATTAGCGTCATCAT 5220  
-----+-----+-----+-----+-----+  
TTACTAACCTCAATCTTATTAGATGATATCCTAGTATAAAATAATTTAATCGCAGTAGTA  
d S H N S N S Y D V I P D Y K I L N A D D -

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FIG. 5J

5221 AATATTGCCTCCATTTTT TAGGGTAATTATCCAGAATTGAAATATCAGATTTAACCATAG 5280  
 -----+-----+-----+-----+-----+-----+-----+-----+  
 TTATAACGGAGGTAAAAATCCCATTAATAGGTCTTAACCTTTATAGTCTAAATTGGTATC  
 d Y Y Q R W K K P Y N D L I S I D S K V M -  
  
 N  
 r  
 u  
 I  
 5281 AATGAGGATAAATGATCGCGAGTAAATAATATTCACAATGTACCATTTTAGTCATATCAG 5340  
 -----+-----+-----+-----+-----+-----+-----+  
 TTACTCCTATTTACTAGCGCTCATTTATTATAAGTGTACATGGTAAAATCAGTATAGTC  
 S H P Y I I A L L Y Y E C H V M K T M D -  
 5341 ATAAGCATTGATTAATATCATTATTGCTTCTACAGGCTTTAATTTTATTAATTATTCTGT 5400  
 -----+-----+-----+-----+-----+-----+-----+  
 TATTCGTAACATAATTAGTAATAACGAAGATGTCCGAAATTAAATAATTAATAAGACA  
 S L C Q N I D N N S R C A K I K N I I R -  
 5401 AAGTGTCTGTCGGCATTATGTCTTTCATACCCATCTCTTTATCCTTACCTATTGTTTGTC 5460  
 -----+-----+-----+-----+-----+-----+-----+  
 TTCACAGCAGCCGTAAATACAGAAAGTATGGGTAGAGAAATAGGAATGGATAACAAACAG  
 Y T D D A N I D K M  
 <---- luxR protein ---|  
 GCAAGTTTTGCGTGTATATATCATTAAAACGGTAATAGATTGACATTTGATTCTAATAA  
 5461 -----+-----+-----+-----+-----+-----+-----+ 5520  
 CGTTCAAAACGCACAATATATAGTAATTTTGCCATTATCTAACTGTAAACTAAGATTATT  
 <-----| <-----| <-----| <----- Promoter (luxPL) -----  
  
 luxR mRNA start sites  
  
 CRP Binding Site  
 -----  
 5521 ATTGGATTTTTGTCACACTATTATATCGCTTGAAATACAATTGTTTAAACATAAGTACCTG 5580  
 -----+-----+-----+-----+-----+-----+-----+  
 TAACCTAAAAACAGTGTGATAATATAGCGAACTTTATGTTAAACAAATTGTATTTCATGGAC  
  
 ----- Promoter (luxPR) -----> C B  
 lux operator site -35 -10 a a  
 -----+-----+-----+-----+-----+-----+-----+  
 TAGGATCGTACAGGTTTACGCAAGAAATGGTTTGTATAGTCGATTAATCGATTTGATT  
 5581 -----+-----+-----+-----+-----+-----+-----+ 5640  
 ATCCTAGCATGTCCAAATGCGTTCCTTTACCAACAATATCAGCTAATTAGCTAAACTAA  
 |---- 1209-85 -----> |-- mRNA start -->  
  
 NdeI  
 |  
 5641 CTAGATTTGTTTAACTAATTAAAGGAGGAATAACATATGATCGCTCCACCATGCACCAG 5700  
 -----+-----+-----+-----+-----+-----+-----+  
 GATCTAAACAAAATTGATTAATTTCTCCTTATTGTATACTAGCGAGGTGGTACGTGGTC  
  
 b M I A P P C T S -  
 |-- RANK -->  
 5701 TGAGAAGCATTATGAGCATCTGGGACGGTGTGTAACAAATGTGAACCAGGAAAGTACAT 5760  
 -----+-----+-----+-----+-----+-----+-----+  
 ACTCTTCGTAATACTCGTAGACCCTGCCACGACATTGTTTACACTTGGTCCTTTCATGTA  
  
 b E K H Y E H L G R C C N K C E P G K Y M -

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FIG. 5K

```

5761  GTCTTCTAAATGCAC TACTACCTCTGACAGTGTATGTCTGCCCTGTGGCCCGGATGAATA
      +-----+-----+-----+-----+-----+
5820  CAGAAGATTTACGTGATGATGGAGACTGTACATACAGACGGGACACCGGGCCTACTTAT
b    S S K C T T T S D S V C L P C G P D E Y -

      CTTGGATAGCTGGAATGAAGAAGATAAATGCTTGCTGCATAAAGTTTGTGATACAGGCAA
5821  +-----+-----+-----+-----+-----+
5880  GAACCTATCGACCTTACTTCTTCTATTTACGAACGACGTATTTCAAACACTATGTCCGTT
b    L D S W N E E D K C L L H K V C D T G K -

                                     ApaLI
                                     |
5881  GGCCCTGGTGGCCGTGGTCGCCGGCAACAGTACGACCCCCGGCGCTGCGCGTGCACGGC
      +-----+-----+-----+-----+-----+
5940  CCGGGACCACCGGCACCAGCGGCCGTTGTCTATGCTGGGGGGCCGCGACGCGCACGTGCCG
b    A L V A V V A G N S T T P R R C A C T A -

      KpnI
      |
      Acc65I
      |
5941  TGGGTACCACTGGAGCCAGGACTGCGAGTGTGCGCGCCGCAACACCGAGTGC GCGCCGGG
      +-----+-----+-----+-----+-----+
6000  ACCCATGGTGACCTCGGTCCTGACGCTCAGCAGCGCGGCGTGTGGCTCAGCGCGGCC
b    G Y H W S Q D C E C C R R N T E C A P G -

      CCTGGGCGCCCAGCACCCGTTGCAGCTCAACAAGGACACAGTGTGCAAACCTTGCCCTTGC
6001  +-----+-----+-----+-----+-----+
6060  GGACCCGCGGGTCGTGGGCAACGTCGAGTTGTTCTGTGTACACGTTTGAACGGAACG
b    L G A Q H P L Q L N K D T V C K P C L A -

      AGGCTACTTCTCTGATGCCTTTTCTCCACGGACAAATGCAGACCCTGGACCAACTGTAC
6061  +-----+-----+-----+-----+-----+
6120  TCCGATGAAGAGACTACGGAAGAGGAGTGCCTGTTTACGTCTGGGACCTGGTTGACATG
b    G Y F S D A F S S T D K C R P W T N C T -

      CTTCTTGAAAGAGAGTAGAACATCATGGGACAGAGAAATCCGATGTGGTTTGCAGTTC
6121  +-----+-----+-----+-----+-----+
6180  GAAGGAACCTTTCTCTCATCTTGTAGTACCCTGTCTCTTTAGGCTACACCAAACGTCAAG
b    F L G K R V E H H G T E K S D V V C S S -

                                     AccI
                                     |
                                     SalI
                                     |
6181  TTCTCTGCCAGCTAGAAAACCAACCAATGAACCCCATGTTTACGTGACAAAACTCACAC
      +-----+-----+-----+-----+-----+
6240  AAGAGACGGTCGATCTTTTGGTGGTTTACTTGGGGTACAAATGCAGCTGTTTTGAGTGTG
b    S L P A R K P P N E P H V Y V D K T H T -
      <-- end RANK --||--start Fc-->
```

[illegible]



## FIG. 5M

b            Q P E N N Y K T T P P V L D S D G S F F -  
 CCTCTACAGCAAGCTCACCCTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATG  
 6781 -----+-----+-----+-----+-----+ 6840  
 GGAGATGTCGTTCGAGTGGCACCTGTTCTCGTCCACCGTCGTCCCCTTGCAGAAGAGTAC

b            L Y S K L T V D K S R W Q Q G N V F S C -  
 CTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCC  
 6841 -----+-----+-----+-----+-----+ 6900  
 GAGGCACTACGTACTCCGAGACGTGTTGGTGATGTGCGTCTTCTCGGAGAGGGACAGAGG

b            S V M H E A L H N H Y T Q K S L S L S P -  
 BamHI  
 |  
 GGGTAAATAATGGATCCGCGGAAAGAAGAAGAAGAAGAAGCCCGAAAGGAAGCTGA  
 6901 -----+-----+-----+-----+-----+ 6960  
 CCCATTTATTACCTAGGCGCCTTTCTTCTTCTTCTTCTTCTTCGGGCTTTCCTTCGACT

b            G K \*  
 BspI  
 |  
 GTTGGCTGCTGCCACCGCTGAGCAATAACTAGCATAACCCCTTGGGGCCTCTAAACGGGT  
 6961 -----+-----+-----+-----+-----+ 7020  
 CAACCGACGACGGTGGCGACTCGTTATTGATCGTATTGGGGAACCCCGGAGATTGCCCCA  
 <----->  
 CTTGAGGGGTTTTTTTGCTGAAAGGAGGAACCGCTCTTCACGCTCTTCACGCGGATAAATA  
 7021 -----+-----+-----+-----+-----+ 7080  
 GAACTCCCCAAAAACGACTTTCCTCCTTGGCGAGAAGTGCGAGAAGTGCGCCTATTTAT  
 -T7 stop ---->|

toop hairpin  
 ----->  
 AGTAACGATCCGGTCCAGTAATGACCTCAGAACTCCATCTGGATTGTTCAGAACGCTCG  
 7081 -----+-----+-----+-----+-----+ 7140  
 TCATTGCTAGGCCAGGTCATTACTGGAGTCTTGAGGTAGACCTAAACAAGTCTTGCGAGC

toop hairpin  
 <----->  
 GTTGCCGCGGGCGTTTTTTTATTGGTGAGAATCGCAGCAACTTGTGCGCCAATCGAGCC  
 7141 -----+-----+-----+-----+-----+ 7200  
 CAACGGCGGCGCCGCAAAAAATAACCACTCTTAGCGTCGTTGAACAGCGCGGTTAGCTCGG  
 -- toop stop -->|

ATGTCGTCGTCAACGACCCCCCATTCAGAACAAGCAAGCAGCATTGAGAACTTTGGAATC  
 7201 -----+-----+-----+-----+-----+ 7260  
 TACAGCAGCAGTTGCTGGGGGGTAAGTTCTTGTCGTTCTGTCGTAACCTTTGAAACCTTAG  
 CAGTCCCTCTTCCACCTGCTGACCG  
 7261 -----+-----+-----+-----+ 7285  
 GTCAGGGAGAAGGTGGACGACTGGC

FIG. 6A

[AatII sticky end] 5' GCGTAACGTATGCATGGTCTCC-  
(position #4358 in pAMG21) 3' TGCACGCATTGCATACGTACCAGAGG-

-CCATGCGAGAGTAGGGAACTGCCAGGCATCAAATAAACGAAAGGCTCAGTCGAAAGACT-  
-GGTACGCTCTCATCCCTTGACGGTCCGTAGTTATTTTGCTTTCCGAGTCAGCTTTCTGA-

-GGGCCTTTTCGTTTTATCTGTTGTTGTCGGTGAACGCTCTCCTGAGTAGGACAAATCCGC-  
-CCCGGAAAGCAAAATAGACAACAAACAGCCACTTGCGAGAGGACTCATCTGTTTAGGCG-

-CGGGAGCGGATTTGAACGTTGCGAAGCAACGCGCCGGAGGGTGGCGGGCAGGACGCCCGC-  
-GCCCTCGCTTAACTTGCAACGCTTCGTTGCCGGGCCCTCCACCGCCCGTCTTGGGGCG-

-CATAAATGCCAGGCATCAAATTAAGCAGAAGGCCATCTGACGGATGGCCTTTTTCGCT-  
-GTATTTGACGGTCCGTAGTTAATTCGTCTTCCGGTAGGACTGCCACCGGAAAAACGCA-

AatII

-TTCTACAACTCTTTTGTATTATTTTCTAAATACATTCAAATATGGACGTCGTACTTAAC-  
-AAGATGTTTGAGAAAACAAATAAAAGATTATGTAAGTTTATACCTGCAGCATGAATTG-

-TTTAAAGTATGGGCAATCAATTGCTCCTGTTAAATTGCTTTAGAAATACTTTGGCAGC-  
-AAAATTCATACCCGTTAGTTAACGAGGACAATTTTAACGAAATCTTTATGAAACCGTCG-

-GGTTTGTGATTGAGTTTCATTTGCGCATTTGGTTAAATGGAAAGTGACCGTGCGCTTAC-  
-CCAAACAACATAACTCAAAGTAAACGCGTAACCAATTACCTTTCACCTGGCACGCGAATG-

-TACAGCCTAATATTTTGAATATCCCAAGAGCTTTTTCCTTCGCATGCCCACGCTAAAC-  
-ATGTCGATTATAAAAACCTTTATAGGGTTCTCGAAAAAGGAAGCGTACGGGTGCGATTG-

-ATTCTTTTCTCTTTTGGTTAAATCGTTGTTGATTATTATTGCTATATTTATTTTTC-  
-TAAGAAAAAGAGAAAACCAATTTAGCAACAACTAAATAATAACGATATAAATAAAAG-

-GATAATTATCAACTAGAGAAGGAACAATTAATGGTATGTTTCATACACGCATGTAAAAATA-  
-CTATTAATAGTTGATCTCTTCTTGTAAATACCATACAAGTATGTGCGTACATTTTTAT-

-AACTATCTATATAGTTGTCTTCTCTGAATGTGCAAACTAAGCATTCCGAAGCCATTAT-  
-TTGATAGATATATCAACAGAAAGAGACTTACACGTTTGTATTGTAAGGCTTCGGTAATA-

-TAGCAGTATGAATAGGGAACATAAACCCAGTGATAAGACCTGATGATTTCGCTTCTTTAA-  
-ATCGTCATACTTATCCCTTTGATTGGGTCACTATTCTGGACTACTAAAGCGAAGAAATT-

-TTACATTTGGAGATTTTTTATTACAGCATTTGTTTCAAATATATTCCAATTAATCGGTG-  
-AATGTAAACCTCTAAAAAATAAATGTCGTAACAAAAGTTTATATAAGGTTAATTAGCCAC-

-AATGATTGGAGTTAGAATAATCTACTATAGGATCATATTTTATTAAATTAGCGTCATCAT-  
-TTACTAACCTCAATCTTATTAGATGATATCCTAGTATAAAATAATTTAATCGCAGTAGTA-

-AATATTGCCTCCATTTTTTAGGGTAATTATCCAGAATTGAAATATCAGATTAAACCATAG-  
-TTATAACGGAGGTAAAAAATCCCATTAATAGGTCTTAACTTTATAGTCTAAATTGGTATC-

-AATGAGGATAAATGATCGCGAGTAAATAATATTCACAATGTACCATTTTAGTCATATCAG-  
-TTACTCCTATTTACTAGCGCTCATTTATTATAAGTGTTACATGGTAAATCAGTATAGTC-

-ATAAGCATTGATTAAATATCATTTATTGCTTCTACAGGCTTTAATTTTATTAATTATTCTGT-  
-TATTCGTAACATAATTATAGTAATAACGAAGATGTCCGAAATTAAAAATAATTAATAAGACA-

-AAGTGTGCTCGGCATTTATGTCTTTCATACCCATCTCTTTATCCTTACCTATTGTTTGTG-  
-TTCACAGCAGCCGTAAATACAGAAAGTATGGGTAGAGAAATAGGAATGGATAACAAACAG-

-GCAAGTTTTGCGTGTATATATCATTAATAACGGTAATAGATTGACATTTGATTCTAATAA-  
-CGTTCAAAACGCACAATATATAGTAATTTGCCATTATCTAACTGTAACTAAGATTATT-

## FIG. 6B

-ATTGGATTTTTGTCACACTATTATATCGCTTGAAATACAATTGTTTAAACATAAGTACCTG-  
-TAACCTAAAAACAGTGTGATAATATAGCGAACTTTATGTTAACAAATTGTATTCATGGAC-  
-TAGGATCGTACAGGTTTACGCAAGAAAATGGTTTGTATAGTCGATTAATCGATTTGATT-  
-ATCCTAGCATGTCCAAATGCGTTCTTTTACCAACAATATCAGCTAATTAGCTAAACTAA-  
-CTAGATTTGTTTTAACTAATTAAAGGAGGAATAACATATGGTTAACGCGTTGGAATTCGA-  
-GATCTAAACAAAATTGATTAATTCCTCCTTATTGTATACCAATTGCGCAACCTTAAGCT-  
-GCTCACTAGTGTGACCTGCAGGGTACCATGGAAGCTTACTCGAGGATCCGCGGAAAGAA-  
-CGAGTGATCACAGCTGGACGTCCCATGGTACCTTCGAATGAGCTCCTAGGCGCCTTCTT-  
-GAAGAAGAAGAAGAAAGCCCGAAAGGAAGCTGAGTTGGCTGCTGCCACCGCTGAGCAATA-  
-CTTCTTCTTCTTCTTTCGGGCTTTCCTTCGACTCAACCGACGACGGTGGCGACTCGTTAT-  
-ACTAGCATAACCCCTTGGGGCCTCTAAACGGGTCTTGAGGGGTTTTTTGCTGAAAGGAGG-  
-TGATCGTATTGGGGAACCCCGGAGATTTGCCCAGAACTCCCCAAAAAACGACTTTCCTCC-  
-AACCGCTCTTCACGCTCTTCACGC 3' [SacII sticky end]  
-TTGGCGAGAAGTGCGAGAAGTG 5' (position #5904 in pAMG21)

FIG. 7

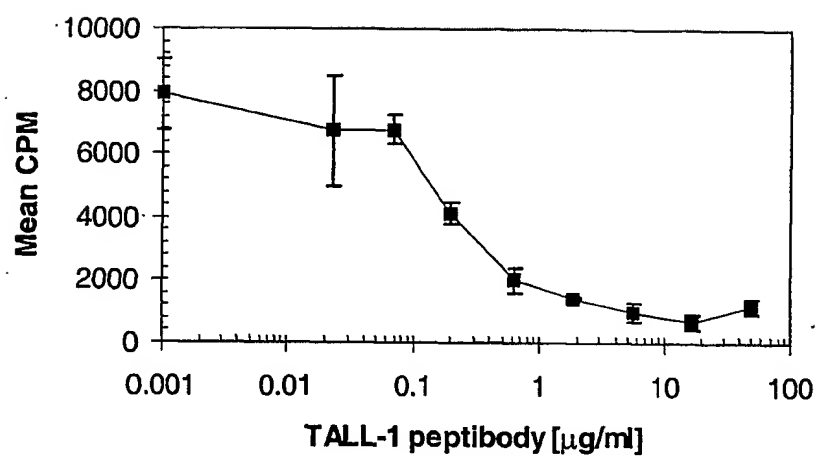


FIG. 8

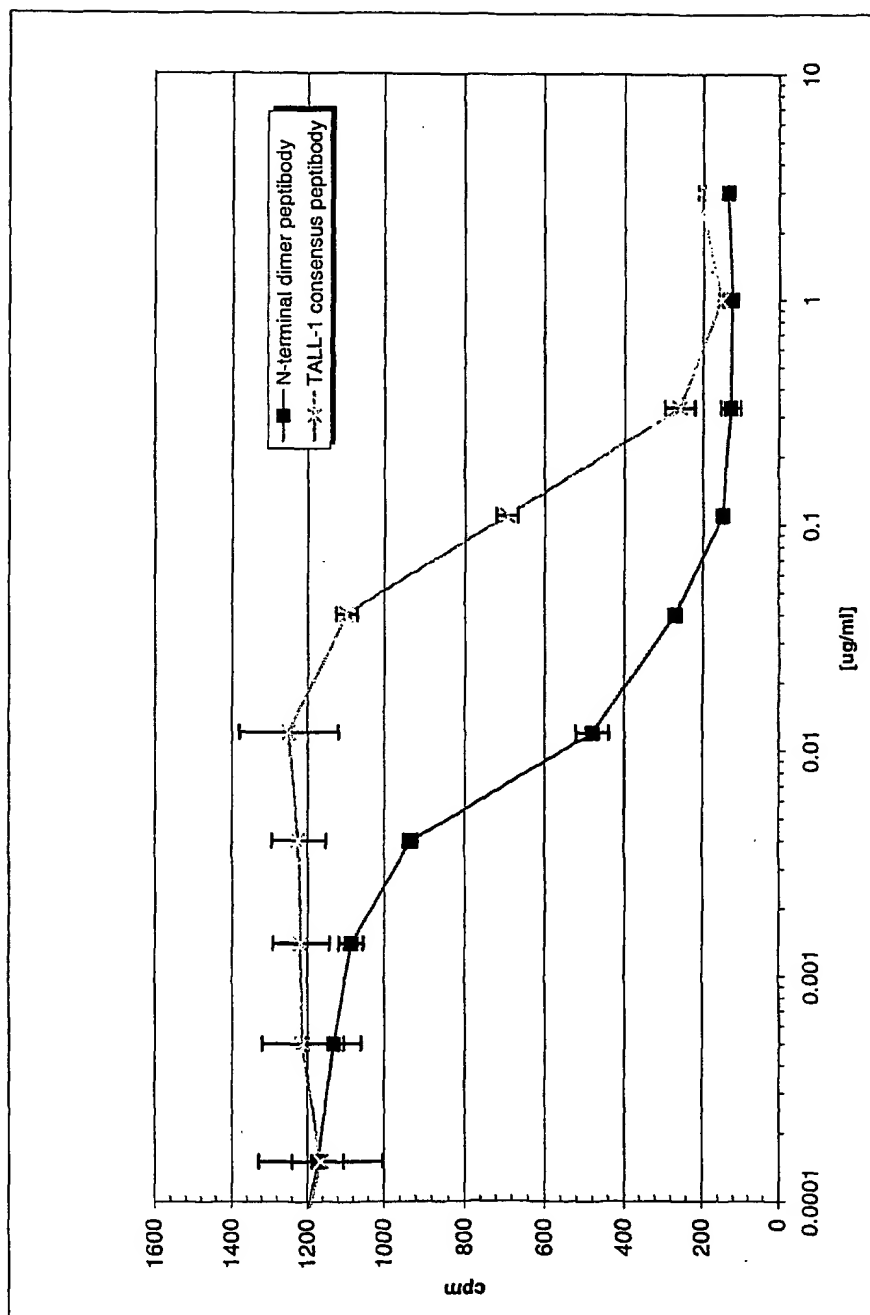


FIG. 9

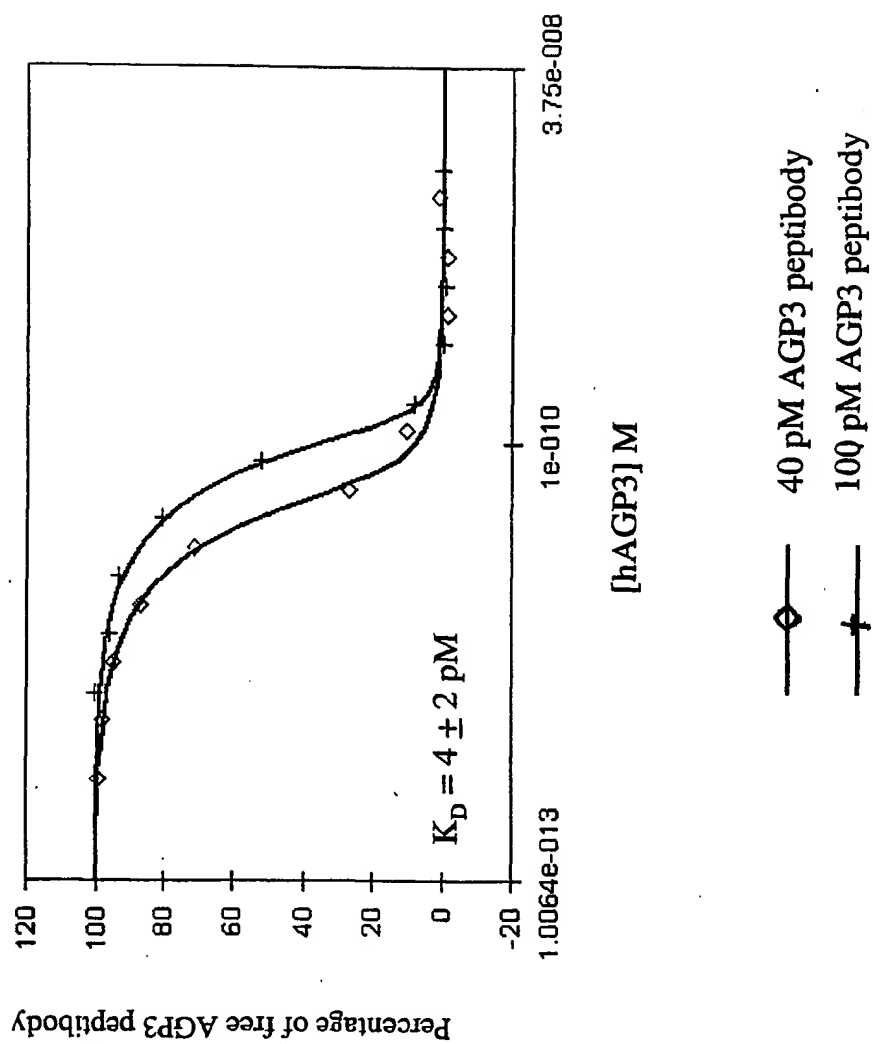


FIG. 10A

Against human AGP3

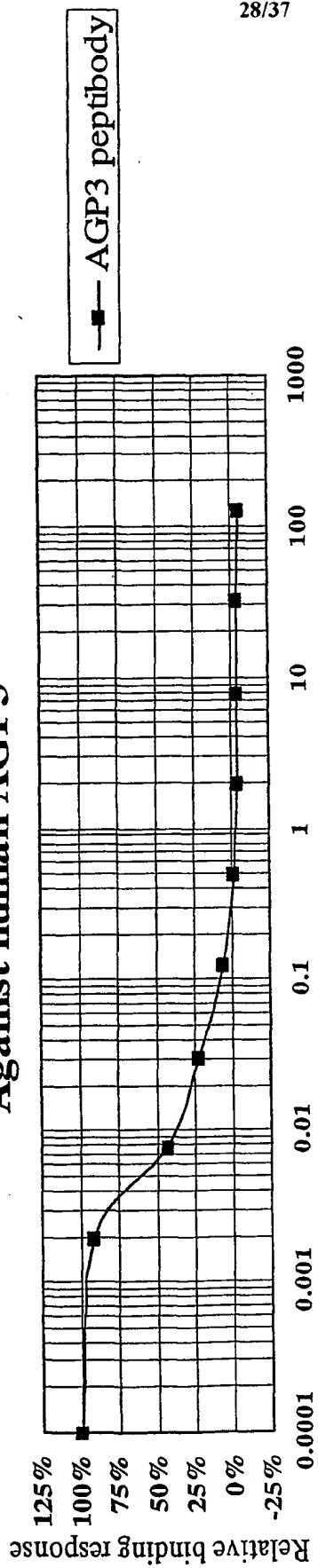


FIG. 10B

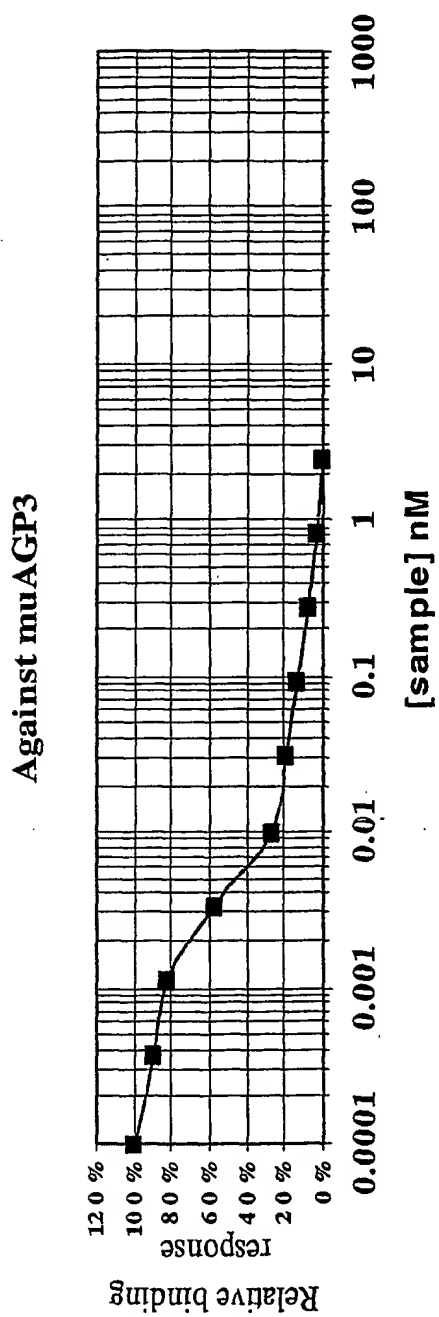




FIG. 11A

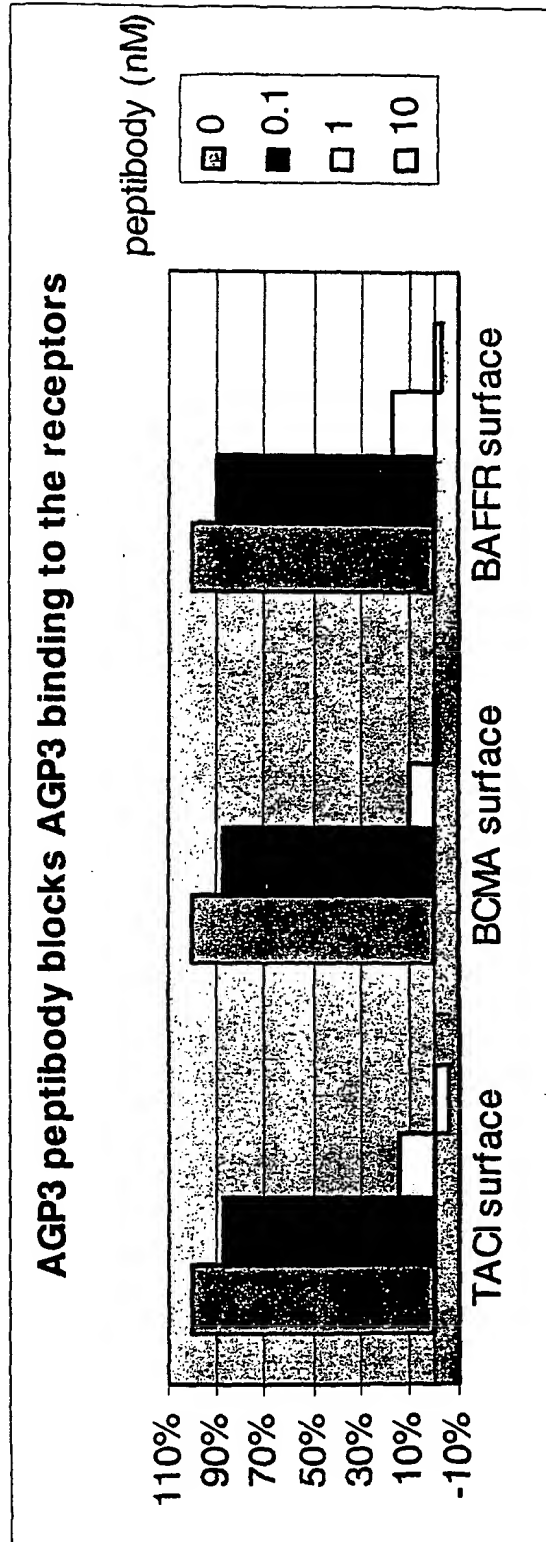


FIG. 11B

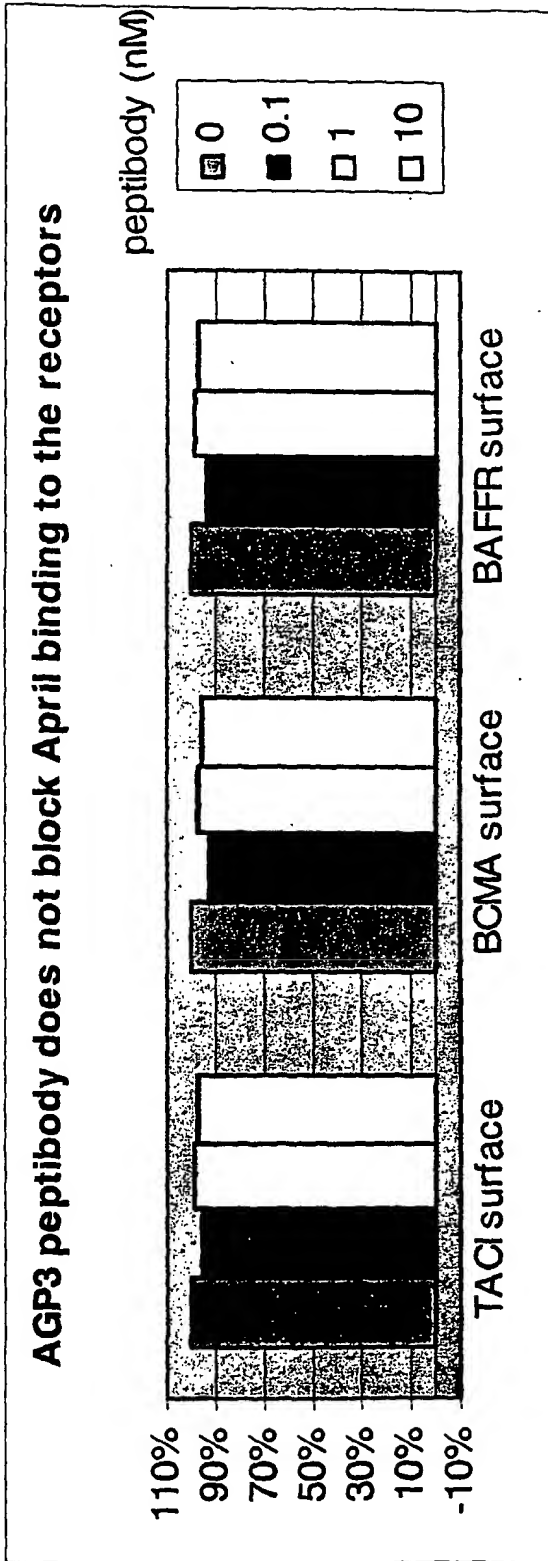


FIG. 12B

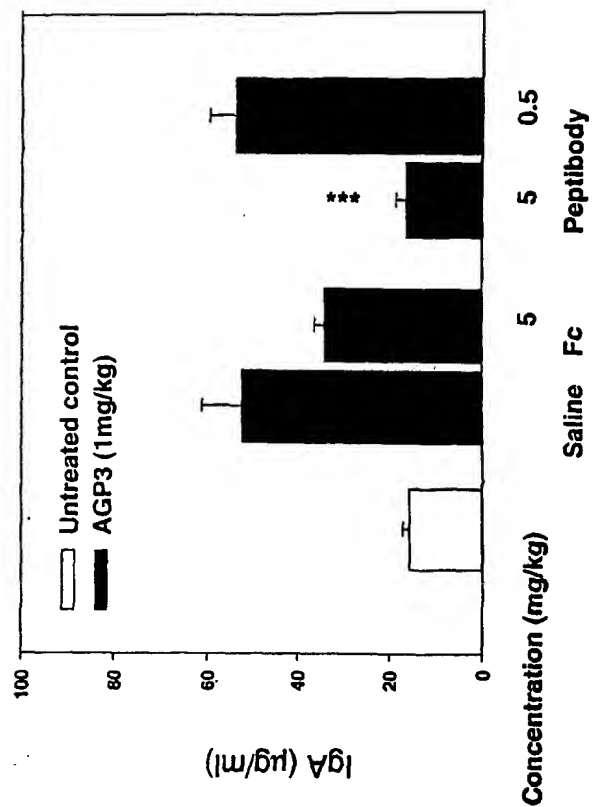


FIG. 12A

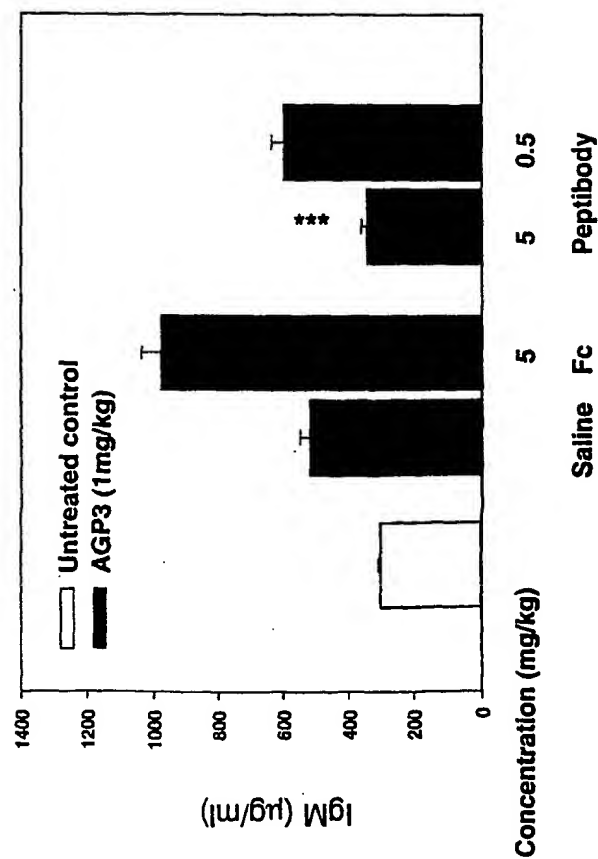
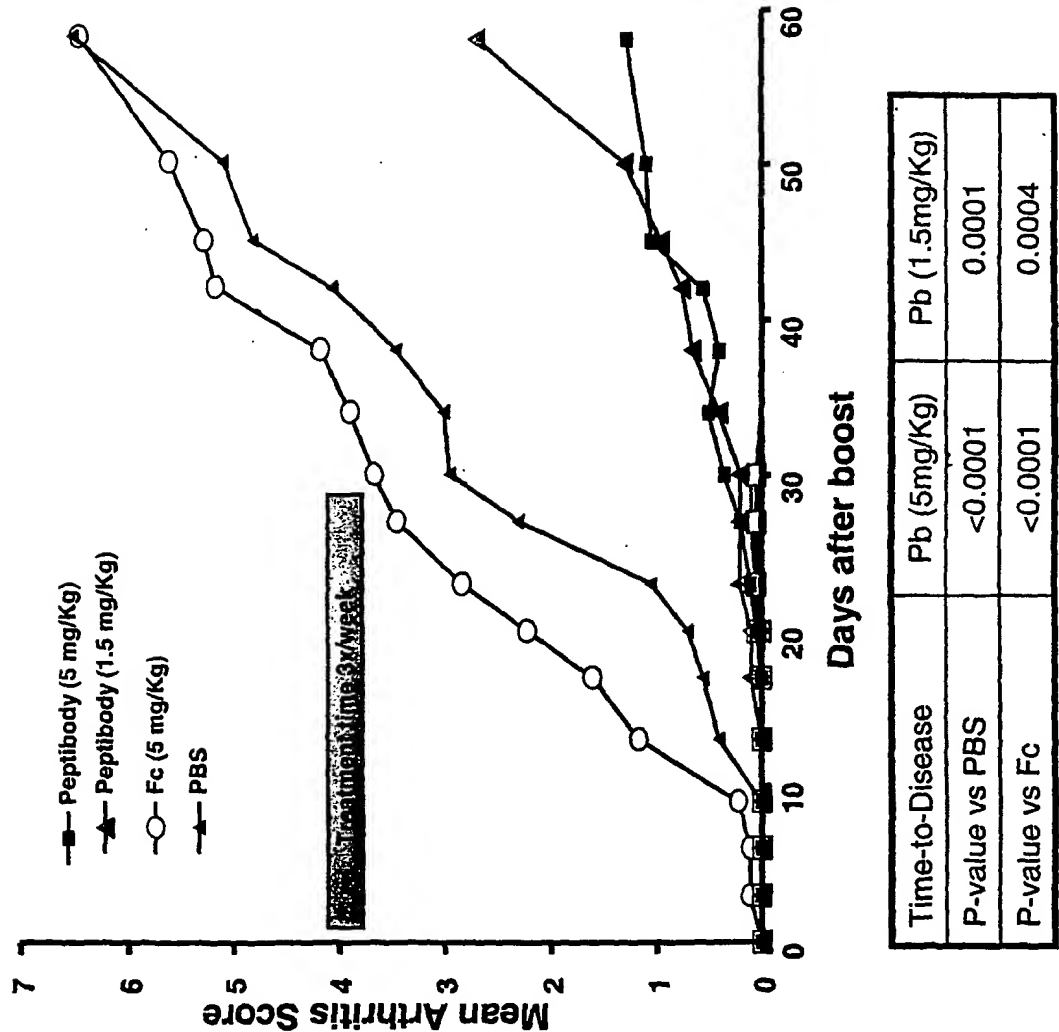


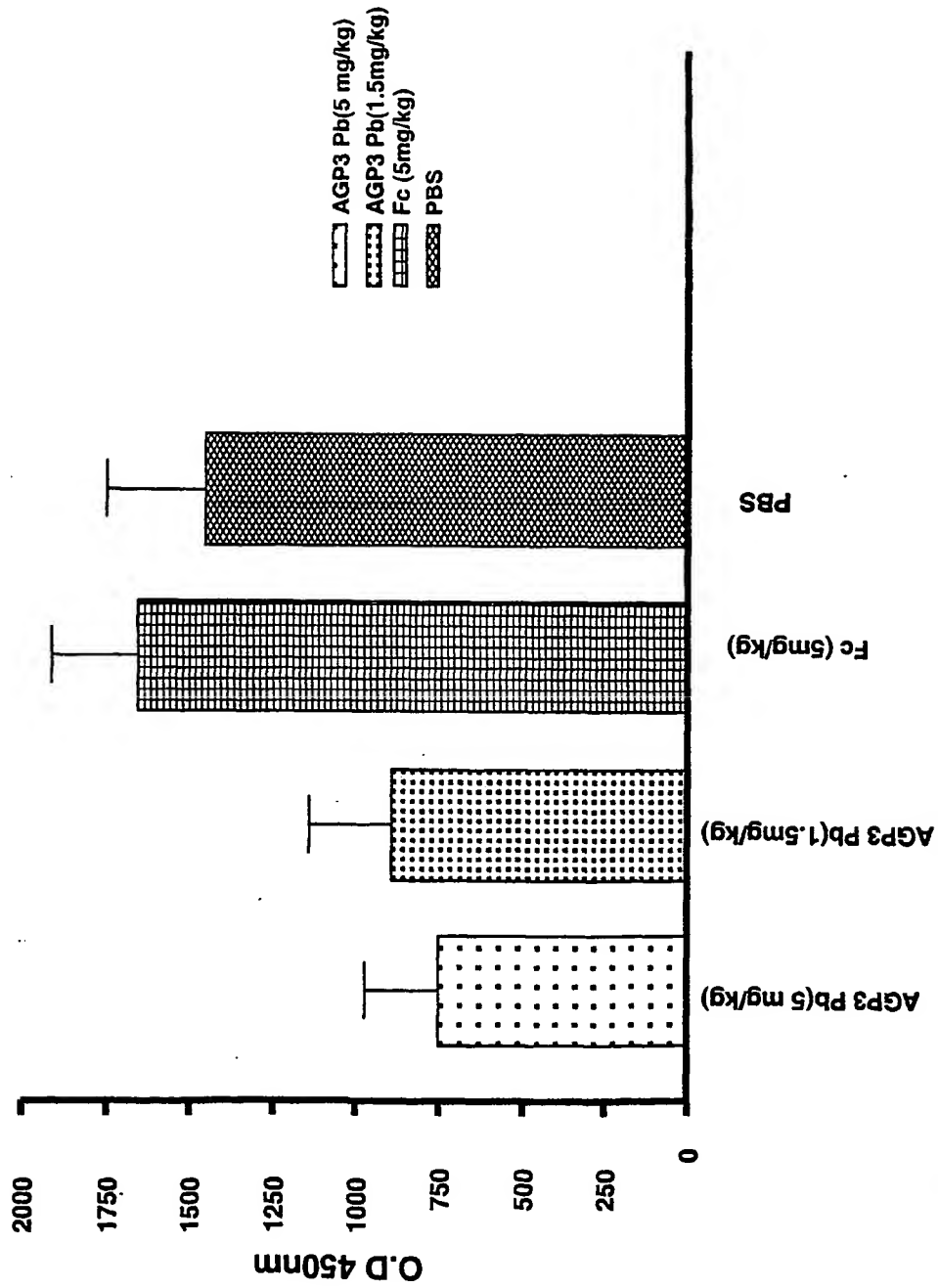
FIG. 13



Note: p-value based on log-rank test

FIG. 14

Reduced anti-collagen IgG2b upon  
treatment with AGP3 peptibody



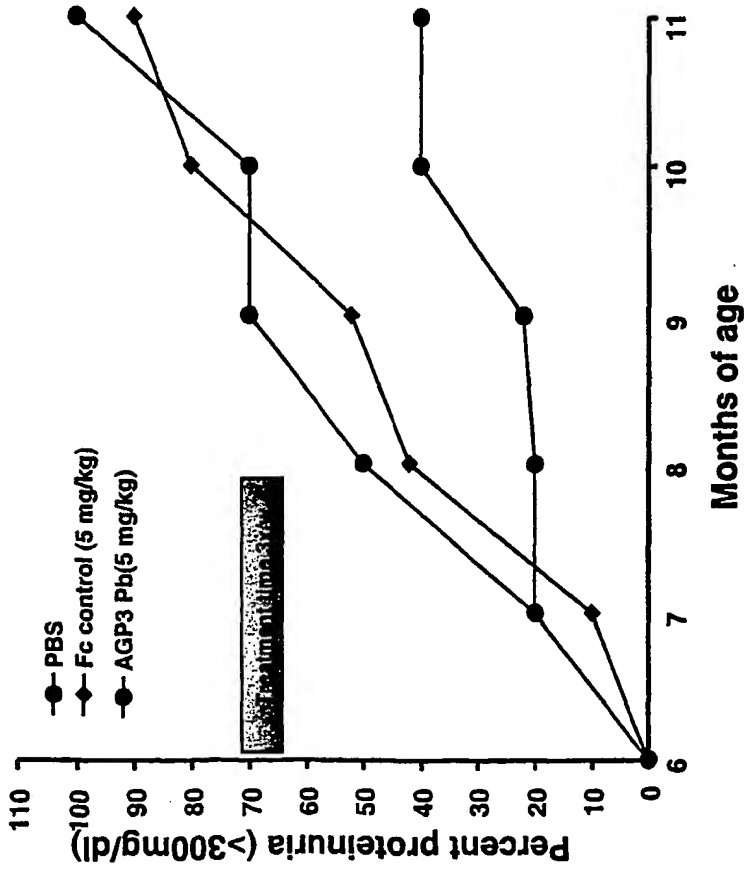
Serum samples were taken one week after final treatment of reagent (day 35).

The graph above is representative of the IgG1, IgG3, and IgG2a isotypes as well.

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Fig. 15A

Delayed proteinuria with AGP3 protein blockers

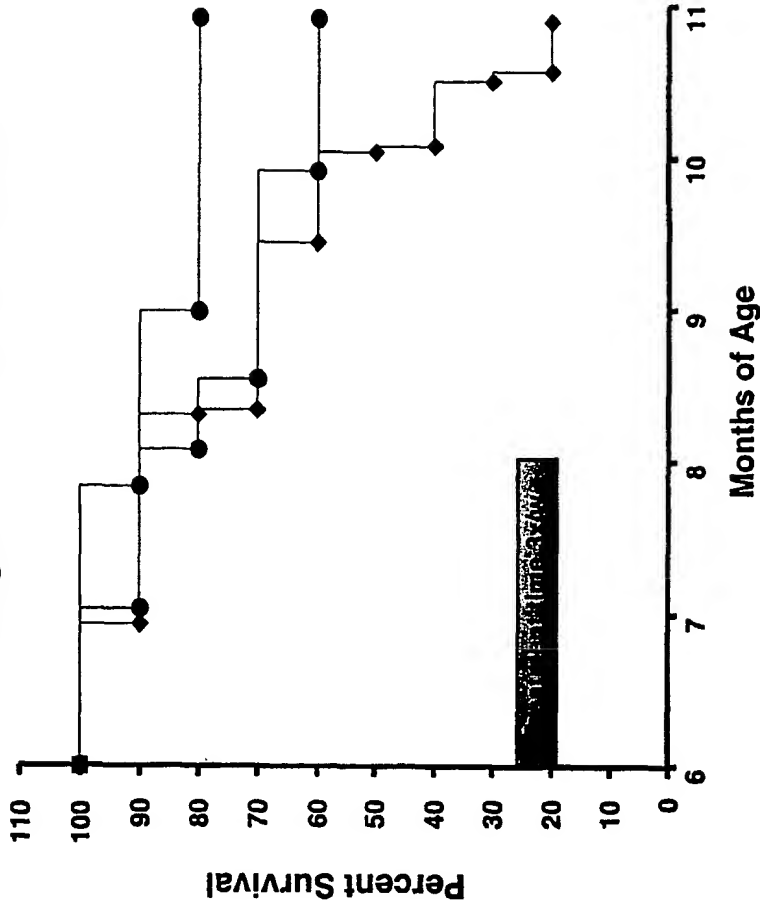


| Proteinuria Incidence | Pb     |
|-----------------------|--------|
| p-value vs PBS        | 0.0108 |
| P-vs Fc               | 0.0573 |

P-value based Fisher's Exact test

Fig. 15B

Prolonged survival with AGP3 blockers



| Time-to-Death  | Pb     |
|----------------|--------|
| p-value vs PBS | 0.3685 |
| p-value vs Fc  | 0.0159 |

P-value based log-rank test

## FIG. 16A

BamHI  
|

1 ATGCTTCCAGGCTGCAAGTGGGATCTTCTTATTAAGCAATGGGTATGCGATCCACTTGGA  
-----+-----+-----+-----+-----+ 60  
TACGAAGGTCCGACGTTACCCTAGAGAATAATTCGTTACCCATACGCTAGGTGAACCT

M L P G C K W D L L I K Q W V C D P L G -

61 TCCGGTTCCTGCTACTGGTGGTTCGGGCTCCACCGCAAGCTCTGGTTCAGGCAGTGCCTG  
-----+-----+-----+-----+-----+ 120  
AGGCCAAGACGATGACCACCAAGGCCGAGGTGGCGTTCGAGACCAAGTCCGTCACGCTGA

S G S A T G G S G S T A S S G S G S A T -

NdeI  
|

121 CATATGCTGCCGGGTGTAAATGGGACCTGCTGATCAAACAGTGGGTTTGTGACCCGCTG  
-----+-----+-----+-----+-----+ 180  
GTATACGACGGCCCAACATTTACCCTGGACGACTAGTTTGTACCCAAACACTGGGCGAC

H M L P G C K W D L L I K Q W V C D P L -

SalI  
|

181 GGTGGAGGCGGTGGGGTCGACAAACTCACACATGTCCACCTTGTCCAGCTCCGGAATC  
-----+-----+-----+-----+-----+ 240  
CCACCTCCGCCACCCAGCTGTTTTGAGTGTGTACAGGTGGAACAGGTGAGGCCTTGAG

G G G G G V D K T H T C P P C P A P E L -

241 CTGGGGGACCGTCAGTCTTCTCTTCCCCCAAACCAAGGACACCCTCATGATCTCC  
-----+-----+-----+-----+-----+ 300  
GACCCCCCTGGCAGTCAGAAGGAGAAGGGGGTTTTGGGTTCTGTGGGAGTACTAGAGG

L G G P S V F L F P P K P K D T L M I S -

301 CGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAG  
-----+-----+-----+-----+-----+ 360  
GCCTGGGGACTCCAGTGTACGCACCACCACCTGCACTCGGTGCTTCTGGGACTCCAGTTC

R T P E V T C V V V D V S H E D P E V K -

361 TTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAG  
-----+-----+-----+-----+-----+ 420  
AAGTTGACCATGCACCTGCCGCACCTCCACGTATTACGGTTCGTTCGGCGCCCTCCTC

F N W Y V D G V E V H N A K T K P R E E -

421 CAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTG  
-----+-----+-----+-----+-----+ 480  
GTCATGTTGTGTCGTGCATGGCACCAGTCGCAGGAGTGGCAGGACGTGGTCTGACCGAC

Q Y N S T Y R V V S V L T V L H Q D W L -

**FIG. 16B**

AATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAA  
481 -----+-----+-----+-----+-----+-----+-----+ 540  
TTACCGTTCCCTCATGTTACGTTCCAGAGGTTGTTTCGGGAGGGTCGGGGGTAGCTCTTT  
N G K E Y K C K V S N K A L P A P I E K -  
ACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCC  
541 -----+-----+-----+-----+-----+-----+-----+ 600  
TGGTAGAGGTTTCGGTTTCCCGTCGGGGCTCTTGGTGTCCACATGTGGGACGGGGGTAGG  
T I S K A K G Q P R E P Q V Y T L P P S -  
CGGGATGAGCTGACCAAGAACCAGGTGAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCC  
601 -----+-----+-----+-----+-----+-----+-----+ 660  
GCCCTACTCGACTGGTTCTTGGTCCAGTCGGACTGGACGGACCAGTTTCCGAAGATAGGG  
R D E L T K N Q V S L T C L V K G F Y P -  
AGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGAGAACAACTACAAGACCACG  
661 -----+-----+-----+-----+-----+-----+-----+ 720  
TCGCTGTAGCGGCACCTCACCCCTCTCGTTACCCGTCGGCCTCTTGTGATGTTCTGGTGC  
S D I A V E W E S N G Q P E N N Y K T T -  
CCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAG  
721 -----+-----+-----+-----+-----+-----+-----+ 780  
GGAGGGCACGACCTGAGGCTGCCGAGGAAGAAGGAGATGTCGTTTCGAGTGGCACCTGTTC  
P P V L D S D G S F F L Y S K L T V D K -  
AGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAAC  
781 -----+-----+-----+-----+-----+-----+-----+ 840  
TCGTCCACCGTCGTCCCTTGCAGAAGAGTACGAGGCACTACGTACTCCGAGACGTGTTG  
S R W Q Q G N V F S C S V M H E A L H N -  
CACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATAA  
841 -----+-----+-----+-----+-----+-----+ 882  
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| atg | gac | aaa | act | cac | aca | tgt | cca | cct | tgt | cca | gct | ccg | gaa | ctc | ctg | 48 |
| Met | Asp | Lys | Thr | His | Thr | Cys | Pro | Pro | Cys | Pro | Ala | Pro | Glu | Leu | Leu |    |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |    |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |    |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|
| ggg | gga | ccg | tca | gtc | ttc | ctc | ttc | ccc | cca | aaa | ccc | aag | gac | acc | ctc | 96 |
| Gly | Gly | Pro | Ser | Val | Phe | Leu | Phe | Pro | Pro | Lys | Pro | Lys | Asp | Thr | Leu |    |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |    |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| atg | atc | tcc | cgg | acc | cct | gag | gtc | aca | tgc | gtg | gtg | gtg | gac | gtg | agc | 144 |
| Met | Ile | Ser | Arg | Thr | Pro | Glu | Val | Thr | Cys | Val | Val | Val | Asp | Val | Ser |     |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| cac | gaa | gac | cct | gag | gtc | aag | ttc | aac | tgg | tac | gtg | gac | ggc | gtg | gag | 192 |
| His | Glu | Asp | Pro | Glu | Val | Lys | Phe | Asn | Trp | Tyr | Val | Asp | Gly | Val | Glu |     |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| gtg | cat | aat | gcc | aag | aca | aag | ccg | cgg | gag | gag | cag | tac | aac | agc | acg | 240 |
| Val | His | Asn | Ala | Lys | Thr | Lys | Pro | Arg | Glu | Glu | Gln | Tyr | Asn | Ser | Thr |     |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| tac | cgt | gtg | gtc | agc | gtc | ctc | acc | gtc | ctg | cac | cag | gac | tgg | ctg | aat | 288 |
| Tyr | Arg | Val | Val | Ser | Val | Leu | Thr | Val | Leu | His | Gln | Asp | Trp | Leu | Asn |     |
|     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| ggc | aag | gag | tac | aag | tgc | aag | gtc | tcc | aac | aaa | gcc | ctc | cca | gcc | ccc | 336 |
| Gly | Lys | Glu | Tyr | Lys | Cys | Lys | Val | Ser | Asn | Lys | Ala | Leu | Pro | Ala | Pro |     |
|     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| atc | gag | aaa | acc | atc | tcc | aaa | gcc | aaa | ggg | cag | ccc | cga | gaa | cca | cag | 384 |
| Ile | Glu | Lys | Thr | Ile | Ser | Lys | Ala | Lys | Gly | Gln | Pro | Arg | Glu | Pro | Gln |     |
|     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| gtg | tac | acc | ctg | ccc | cca | tcc | cgg | gat | gag | ctg | acc | aag | aac | cag | gtc | 432 |
| Val | Tyr | Thr | Leu | Pro | Pro | Ser | Arg | Asp | Glu | Leu | Thr | Lys | Asn | Gln | Val |     |
|     |     | 130 |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| agc | ctg | acc | tgc | ctg | gtc | aaa | ggc | ttc | tat | ccc | agc | gac | atc | gcc | gtg | 480 |
| Ser | Leu | Thr | Cys | Leu | Val | Lys | Gly | Phe | Tyr | Pro | Ser | Asp | Ile | Ala | Val |     |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |

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| 145   | 150 | 155 | 160 |     |
| gag tgg gag agc aat ggg cag ccg gag aac aac tac aag acc acg cct |     |     |     | 528 |
| Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro |     |     |     |     |
|   | 165 | 170 | 175 |     |
| ccc gtg ctg gac tcc gac ggc tcc ttc ttc ctc tac agc aag ctc acc |     |     |     | 576 |
| Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr |     |     |     |     |
|   | 180 | 185 | 190 |     |
| gtg gac aag agc agg tgg cag cag ggg aac gtc ttc tca tgc tcc gtg |     |     |     | 624 |
| Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val |     |     |     |     |
|   | 195 | 200 | 205 |     |
| atg cat gag gct ctg cac aac cac tac acg cag aag agc ctc tcc ctg |     |     |     | 672 |
| Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu |     |     |     |     |
|   | 210 | 215 | 220 |     |
| tct ccg ggt aaa   |     |     |     | 684 |
| Ser Pro Gly Lys   |     |     |     |     |
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| Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu |  |
| 20 25 30  |  |
| Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser |  |
| 35 40 45  |  |
| His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu |  |
| 50 55 60  |  |
| Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr |  |
| 65 70 75 80   |  |
| Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn |  |
| 85 90 95  |  |
| Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro |  |
| 100 105 110   |  |
| Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln |  |
| 115 120 125   |  |
| Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val |  |
| 130 135 140   |  |
| Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val |  |
| 145 150 155 160   |  |

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Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro  
                                   165                                  170                                  175

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr  
                                   180                                  185                                  190

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val  
                                   195                                  200                                  205

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Ser Pro Gly Lys  
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   Met Pro Gly Thr Cys Phe Pro Phe Pro Trp Glu Cys Thr His Ala Gly  
   1                                  5                                  10                                  15

gga ggc ggt ggg g 62  
 Gly Gly Gly Gly  
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   1                                  5                                  10                                  15

Gly Gly Gly Gly  
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|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|
| t   | atg | tgg | ggt | gct | tgt | tgg | ccg | ttc | ccg | tgg | gaa | tgt | ttc | aaa | gaa | ggt | 49 |
| Met | Trp | Gly | Ala | Cys | Trp | Pro | Phe | Pro | Trp | Glu | Cys | Phe | Lys | Glu | Gly |     |    |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |     |    |

gga ggc ggt ggg g

Gly Gly Gly Gly

20

62

&lt;210&gt; 6

&lt;211&gt; 20

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

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&lt;400&gt; 6

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|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Trp | Gly | Ala | Cys | Trp | Pro | Phe | Pro | Trp | Glu | Cys | Phe | Lys | Glu | Gly |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

Gly Gly Gly Gly

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&lt;211&gt; 62

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; NdeI to SalI fragments

&lt;220&gt;

&lt;221&gt; CDS

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&lt;400&gt; 7

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|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|
| t   | atg | gtt | ccg | ttc | tgt | gac | ctg | ctg | act | aaa | cac | tgt | ttc | gaa | gct | ggt | 49 |
| Met | Val | Pro | Phe | Cys | Asp | Leu | Leu | Thr | Lys | His | Cys | Phe | Glu | Ala | Gly |     |    |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |     |    |

gga ggc ggt ggg g

Gly Gly Gly Gly

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62

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&lt;400&gt; 9

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 1 5 10 15

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&lt;223&gt; NdeI to SalI fragments

&lt;400&gt; 10

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Phe His His Gly Gly Gly Gly Gly  
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&lt;210&gt; 11

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act tct tct ggt gga ggc ggt ggg g 74  
 Thr Ser Ser Gly Gly Gly Gly Gly  
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 Gln Phe Asn Gly Val Glu Ala Val  
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cac ggt ctg ggt gga ggc ggt ggg g 74  
 His Gly Leu Gly Gly Gly Gly Gly  
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His Gly Leu Gly Gly Gly Gly Gly  
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|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |    |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|
| t   | atg | cgt | aac | cac | tgt | ttc | tgg | gac | cac | ctg | ctg | aaa | cag | gac | atc | tgt | 49 |
| Met | Arg | Asn | His | Cys | Phe | Trp | Asp | His | Leu | Leu | Lys | Gln | Asp | Ile | Cys |     |    |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |     |    |

|     |     |     |     |     |     |     |     |   |    |
|-----|-----|-----|-----|-----|-----|-----|-----|---|----|
| ccg | tct | ccg | ggt | gga | ggc | ggt | ggg | g | 74 |
| Pro | Ser | Pro | Gly | Gly | Gly | Gly | Gly |   |    |
|     |     |     | 20  |     |     |     |     |   |    |

&lt;210&gt; 22

&lt;211&gt; 24

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; NdeI to SalI fragments

&lt;400&gt; 22

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Arg | Asn | His | Cys | Phe | Trp | Asp | His | Leu | Leu | Lys | Gln | Asp | Ile | Cys |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Ser | Pro | Gly | Gly | Gly | Gly | Gly |
|     |     |     | 20  |     |     |     |     |

&lt;210&gt; 23

&lt;211&gt; 74

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; NdeI to SalI fragments

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (2)..(73)

&lt;223&gt;

&lt;400&gt; 23

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |    |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|
| t   | atg | gct | aac | cag | tgt | tgg | tgg | gac | tct | ctg | ctg | aaa | aaa | aac | gtt | tgt | 49 |
| Met | Ala | Asn | Gln | Cys | Trp | Trp | Asp | Ser | Leu | Leu | Lys | Lys | Asn | Val | Cys |     |    |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |     |    |

|     |     |     |     |     |     |     |     |   |    |
|-----|-----|-----|-----|-----|-----|-----|-----|---|----|
| gaa | ttc | ttc | ggt | gga | ggc | ggt | ggg | g | 74 |
| Glu | Phe | Phe | Gly | Gly | Gly | Gly | Gly |   |    |
|     |     |     | 20  |     |     |     |     |   |    |

&lt;210&gt; 24

&lt;211&gt; 24

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; NdeI to SalI fragments

&lt;400&gt; 24

## A-743 PCT.ST25.txt

Met Ala Asn Gln Cys Trp Trp Asp Ser Leu Leu Lys Lys Asn Val Cys  
 1 5 10 15

Glu Phe Phe Gly Gly Gly Gly  
 20

<210> 25  
 <211> 74  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> NdeI to SalI fragments

<220>  
 <221> CDS  
 <222> (2)..(73)  
 <223>

<400> 25  
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 1 5 10 15

cac ggt ctg ggt gga ggc ggt ggg g 74  
 His Gly Leu Gly Gly Gly Gly Gly  
 20

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 <211> 24  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> NdeI to SalI fragments

<400> 26  
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 1 5 10 15

His Gly Leu Gly Gly Gly Gly Gly  
 20

<210> 27  
 <211> 7285  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> pAMG21-RANK-Fc vector

<400> 27  
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 ggaaacggga aaaagcaagt tttccccgct cccggcgttt caataactga aaaccatact 120  
 atttcacagt ttaaatacaca ttaaacgaca gtaatccccg ttgatttgtg cgccaacaca 180  
 gatcttcgctc acaattctca agtcgctgat ttcaaaaaac tgtagtatcc tctgcgaaac 240  
 gatccctggtt tgagtattga ggaggcgaga tgtcgcagac agaaaatgca gtgacttcct 300

## A-743 PCT.ST25.txt

|             |            |             |            |            |             |      |
|-------------|------------|-------------|------------|------------|-------------|------|
| cattgagtca  | aaagcggttt | gtgcgagag   | gtaagcctat | gactgactct | gagaaacaaa  | 360  |
| tgcccggttg  | tgaagaaaa  | cgtcttacac  | acaagagat  | aaaagttttt | gtcaaaaatc  | 420  |
| ctctgaagga  | tctcatgggt | gagtactgcg  | agagagaggg | gataacacag | gctcagttcg  | 480  |
| ttgagaaaat  | catcaaagat | gaactgcaaa  | gactggatat | actaaagtaa | agactttact  | 540  |
| ttgtggcgta  | gcatgctaga | ttactgatcg  | tttaaggaat | tttgtggctg | gccacgccgt  | 600  |
| aaggtggcaa  | ggaactgggt | ctgatgtgga  | tttacaggag | ccagaaaagc | aaaaaccccg  | 660  |
| ataatcttct  | tcaacttttg | cgagtacgaa  | aagattaccg | gggcccactt | aaaccgtata  | 720  |
| gccacaatt   | cagctatgcg | gggagtatag  | ttatatgcc  | ggaaaagttc | aagacttctt  | 780  |
| tctgtgctcg  | ctccttctgc | gcattgtaag  | tgccagatgg | tgtgactgat | cttcacaaaa  | 840  |
| cgtattaccg  | ccaggtaaag | aacccgaatc  | cgggtgttac | accccgtaga | ggtgcaggaa  | 900  |
| cgtgaagtt   | ctgcgaaaaa | ctgatggaaa  | aggcgggtgg | cttcacttcc | cgttttgatt  | 960  |
| tcgccattca  | tgtggcgcac | gcccgttcgc  | gtgatctgcg | tcgccgatg  | ccaccagtgc  | 1020 |
| tgcgctcgcg  | ggctattgat | gcgctcttgc  | aggggctgtg | tttccactat | gacccgctgg  | 1080 |
| ccaaccgct   | ccagtgtctc | atcaccacgc  | tgccattga  | gtgcggactg | gcgacggagt  | 1140 |
| ctgctgccgg  | aaaactctcc | atcacccgtg  | ccaccgtgc  | cctgacgttc | ctgtcagagc  | 1200 |
| tgggactgat  | tacctaccag | acggaatatg  | acccgcttat | cgggtgctac | attccgaccg  | 1260 |
| atatcacgtt  | cacatctgca | ctgtttgctg  | ccctcgatgt | atcagaggag | gcagtggccg  | 1320 |
| ccgcgcgccg  | cagccgtgtg | gtatgggaaa  | acaacaacg  | caaaaagcag | gggctggata  | 1380 |
| ccctgggcat  | ggatgaactg | atagcgaaag  | cctggcgttt | tgttcgtgag | cgttttcgca  | 1440 |
| gttatcagac  | agagcttaag | tcccgtggaa  | taaagcgtgc | ccgtgcgcgt | cgtgatgcgg  | 1500 |
| acagggaaacg | tcaggatatt | gtcaccctgg  | tgaaacggca | gctgacgcgc | gaaatcgcg   | 1560 |
| aagggcgctt  | cactgccaat | cgtgaggcgg  | taaaacgcga | agttgagcgt | cgtgtgaagg  | 1620 |
| agcgcatgat  | tctgtcacgt | aaccgtaatt  | acagccggct | ggccacagct | tccccctgaa  | 1680 |
| agtacctcc   | tctgaataat | ccggcctgcg  | ccggaggctt | ccgcacgtct | gaagcccgac  | 1740 |
| agcgcacaaa  | aaatcagcac | cacatacaaa  | aaacaacctc | atcatccagc | ttctgggtgca | 1800 |
| tccggcccc   | cctgttttcg | atacaaaaca  | cgcttcacag | acggggaatt | ttgcttatcc  | 1860 |
| acattaaact  | gcaagggact | tcccataag   | gttacaaccg | ttcatgtcat | aaagcgccat  | 1920 |
| cgcgcagcgt  | tacaggggtg | aatgtatctt  | ttaaacacct | gtttatatct | cctttaaact  | 1980 |
| acttaattac  | attcatttaa | aaagaaaacc  | tattcactgc | ctgtccttgg | acagacagat  | 2040 |
| atgcacctcc  | caccgcaagc | ggcgggcccc  | taccggagcc | gctttagtta | caacactcag  | 2100 |
| acacaaccac  | cagaaaaacc | ccggtccagc  | gcagaactga | aaccacaaag | cccctccctc  | 2160 |
| ataactgaaa  | agcggccccc | ccccggtccg  | aagggccgga | acagagtcgc | ttttaattat  | 2220 |
| gaatgttgta  | actacttcat | catcgctgtc  | agtcttctcg | ctggaagttc | tcagtacacg  | 2280 |
| ctcgtaagcg  | gccctgacgg | cccgcataacg | cggagatacg | ccccgacttc | gggtaaacc   | 2340 |

## A-743 PCT.ST25.txt

|             |            |             |             |             |             |      |
|-------------|------------|-------------|-------------|-------------|-------------|------|
| tcgtcgggac  | cactccgacc | gcgcacagaa  | gctctctcat  | ggctgaaagc  | gggtatggtc  | 2400 |
| tggcagggct  | ggggatgggt | aaggtgaaat  | ctatcaatca  | gtaccgggctt | acgccgggct  | 2460 |
| tcggcggttt  | tactcctggt | tcatatatga  | aacaacaggt  | caccgccttc  | catgccgctg  | 2520 |
| atgcggcata  | tcctggtaac | gatatctgaa  | ttgttatata  | tgtgtatata  | cgtggtaatg  | 2580 |
| acaaaaatag  | gacaagttaa | aaatttacag  | gcgatgcaat  | gattcaaaca  | cgtaatcaat  | 2640 |
| atcggggggtg | ggcgaagaac | tccagcatga  | gatccccgcg  | ctggaggatc  | atccagccgg  | 2700 |
| cgtccccgaa  | aacgattccg | aagcccaacc  | tttcatagaa  | ggcggcggtg  | gaatcgaaat  | 2760 |
| ctcgtgatgg  | caggttgggc | gtcgttgggt  | cggtcatttc  | gaacccaga   | gtcccgtca   | 2820 |
| gaagaactcg  | tcaagaaggc | gatagaaggc  | gatgcgctgc  | gaatcgggag  | cggcgatacc  | 2880 |
| gtaaagcacg  | aggaagcggg | cagcccattc  | gccccaagc   | tcttcagcaa  | tatcacgggt  | 2940 |
| agccaacgct  | atgtcctgat | agcggtcgc   | cacaccagc   | cggccacagt  | cgatgaatcc  | 3000 |
| agaaaagcgg  | ccattttcca | ccatgatatt  | cggcaagcag  | gcacgcctat  | gagtcacgac  | 3060 |
| gagatcctcg  | ccgtcgggca | tgcgcgcctt  | gagcctggcg  | aacagttcgg  | ctggcgcgag  | 3120 |
| cccctgatgc  | tcttcgtcca | gatcatcctg  | atcgacaaga  | ccggcttcca  | tccgagtacg  | 3180 |
| tgctcgctcg  | atgcgatggt | tcgcttgggt  | gtcgaatggg  | caggtagccg  | gatcaagcgt  | 3240 |
| atgcagccgc  | cgcattgcat | cagccatgat  | ggatactttc  | tcggcaggag  | caaggtgaga  | 3300 |
| tgacaggaga  | tcctgccccg | gcacttcgcc  | caatagcagc  | cagtcccttc  | ccgcttcagt  | 3360 |
| gacaacgtcg  | agcacagctg | cgcaaggaac  | gcccgtcgtg  | gccagccacg  | atagccgcgc  | 3420 |
| tgccctcgcc  | tgcaattcat | tcaggacacc  | ggacaggtcg  | gtcttgacaa  | aaagaaccgg  | 3480 |
| gcgccccctgc | gctgacagcc | ggaacacggc  | ggcatcagag  | cagccgattg  | tctgttgctg  | 3540 |
| ccagtcatag  | ccgaatagcc | tctccacca   | agcggccgga  | gaacctgcgt  | gcaatccatc  | 3600 |
| ttgttcaatc  | atgcgaaacg | atcctcatcc  | tgtctcttga  | tctgatcttg  | atccccctgcg | 3660 |
| ccatcagatc  | cttggcggca | agaaagccat  | ccagtttact  | ttgcagggct  | tcccaacctt  | 3720 |
| accagagggc  | gccccagctg | gcaattccgg  | ttcgttggct  | gtccataaaa  | ccgccagtc   | 3780 |
| tagctatcgc  | catgtaagcc | cactgcaagc  | tacctgcttt  | ctctttgcgc  | ttgcgttttc  | 3840 |
| ccttgtccag  | atagcccagt | agctgacatt  | catccggggg  | cagcaccggt  | tctgcggact  | 3900 |
| ggctttctac  | gtgttccgct | tccttttagca | gcccttgccg  | cctgagtgtc  | tgccgcagcg  | 3960 |
| tgaagctaca  | tatatgtgat | ccgggcaaat  | cgctgaatat  | tccttttgtc  | tccgaccatc  | 4020 |
| aggcacctga  | gtcgctgtct | ttttcgtgac  | attcagttcg  | ctgcgctcac  | ggctctggca  | 4080 |
| gtgaatgggg  | gtaaatggca | ctacaggcgc  | cttttatgga  | ttcatgcaag  | gaaactaccc  | 4140 |
| ataatacaag  | aaaagcccgt | cacgggcttc  | tcagggcgtt  | ttatggcggg  | tctgctatgt  | 4200 |
| gggtctatct  | gactttttgc | tggttcagcag | ttcctgccct  | ctgattttcc  | agtctgacca  | 4260 |
| cttcggatta  | tcccgtgaca | ggtcattcag  | actggctaata | gcaccagta   | aggcagcggg  | 4320 |
| atcatcaaca  | ggcttaccgg | tcttactgtc  | gaagacgtgc  | gtaacgtatg  | catggctctcc | 4380 |

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| gggccttttcg | ttttatctgt | tgtttgctcg | tgaacgctct | cctgagtagg | acaaatccgc  | 4500 |
| cgggagcgga  | tttgaacgtt | gcgaagcaac | ggcccggagg | gtggcgggca | ggacgcccgc  | 4560 |
| cataaactgc  | caggcatcaa | attaagcaga | aggccatcct | gacggatggc | ctttttgcgt  | 4620 |
| ttctacaaac  | tcttttggtt | atttttctaa | atacattcaa | atatggacgt | cgtacttaac  | 4680 |
| ttttaaagta  | tgggcaatca | attgctcctg | ttaaaattgc | tttagaaata | ctttggcagc  | 4740 |
| ggtttggtgt  | attgagtttc | atttgcgcat | tggttaaatg | gaaagtgacc | gtgcgcttac  | 4800 |
| tacagcctaa  | tatttttgaa | atatcccaag | agctttttcc | ttcgcacgcc | cacgctaaac  | 4860 |
| attctttttc  | tcttttggtt | aaatcgttgt | ttgatttatt | atttgctata | tttatttttc  | 4920 |
| gataattatc  | aactagagaa | ggaacaatta | atgggtatgt | catacacgca | tgtaaaaata  | 4980 |
| aactatctat  | atagttgtct | ttctctgaat | gtgcaaaact | aagcattccg | aagccattat  | 5040 |
| tagcagtatg  | aatagggaaa | ctaaacccag | tgataagacc | tgatgatttc | gcttctttta  | 5100 |
| ttacatttgg  | agatttttta | tttacagcat | tgttttcaaa | tatatcccaa | ttaatcggtg  | 5160 |
| aatgattgga  | gttagaataa | tctactatag | gatcataatt | tattaaatta | gcgtcatcat  | 5220 |
| aatattgcct  | ccatttttta | gggtaattat | ccagaattga | aatatcagat | ttaaccatag  | 5280 |
| aatgaggata  | aatgatcgcg | agtaaataat | attcacaatg | taccatttta | gtcatatcag  | 5340 |
| ataagcattg  | attaatatca | ttattgcttc | tacaggcttt | aattttatta | attattctgt  | 5400 |
| aagtgtcgtc  | ggcatttatg | tctttcatat | ccatctcttt | atccttacct | attgtttgtc  | 5460 |
| gcaagttttg  | cgtgttatat | atcattaaaa | cggtaataga | ttgacatttg | attctaataa  | 5520 |
| attggatttt  | tgtcacacta | ttatatcgct | tgaaatacaa | ttgtttaaca | taagtacctg  | 5580 |
| taggatcgta  | caggtttacg | caagaaaatg | gtttgttata | gtcgattaat | cgatttgatt  | 5640 |
| ctagatttgt  | tttaactaat | taaaggagga | ataacatag  | atcgctccac | catgcaccag  | 5700 |
| tgagaagcat  | tatgagcatc | tgggacggtg | ctgtaacaaa | tgtgaaccag | gaaagtacat  | 5760 |
| gtctttctaaa | tgcactacta | cctctgacag | tgtatgtctg | ccctgtggcc | cggatgaata  | 5820 |
| cttgatagc   | tggaatgaag | aagataaatg | cttgctgcat | aaagtgtgtg | atacaggcaa  | 5880 |
| ggccctggtg  | gccgtggtcg | ccggcaacag | tacgaccccc | cggcgctgcg | cgtgcacggc  | 5940 |
| tgggtaccac  | tggagccagg | actgcgagtg | ctgccgccgc | aacaccgagt | gcgcgccggg  | 6000 |
| cctgggcgcc  | cagcaccctg | tgcagctcaa | caaggacaca | gtgtgcaaac | cttgccctgc  | 6060 |
| aggctacttc  | tctgatgcct | tttcctccac | ggacaaatgc | agaccctgga | ccaactgtac  | 6120 |
| cttccttgga  | aagagagtag | aacatcatgg | gacagagaaa | tccgatgtgg | tttgagtttc  | 6180 |
| ttctctgcc   | gctagaaaac | caccaaata  | acccatggtt | tacgtcgaca | aaactcacac  | 6240 |
| atgtccacct  | tgtccagctc | cggaaactct | ggggggaccg | tcagtcttcc | tcttcccccc  | 6300 |
| aaaacccaag  | gacaccctca | tgatctcccg | gacccttgag | gtcacatgcg | tgggtggtgga | 6360 |
| cgtgagccac  | gaagaccctg | aggtcaagtt | caactggtac | gtggacggcg | tggaggtgca  | 6420 |

## A-743 PCT.ST25.txt

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taatgccaag acaaagccgc gggaggagca gtacaacagc acgtaccgtg tggtcagcgt 6480
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cagtcctctt tccacctgct gaccg 7285

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&lt;210&gt; 28

&lt;211&gt; 7285

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; pAMG21-RANK-Fc vector

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Xaa (Pos1,2,3,15,16,17) are each independently absent or amino acid residues;

Xaa (Pos5,6,7,9,13) are each independently amino acid residues.

&lt;400&gt; 28

Gly Ala Thr Cys Ala Gly Cys Ala Gly Thr Cys Cys Cys Cys Gly Gly  
 1 5 10 15

Ala Ala Cys Ala Thr Cys Gly Thr Ala Gly Cys Thr Gly Ala Cys Gly  
 20 25 30

Cys Cys Thr Thr Cys Gly Cys Gly Thr Thr Gly Cys Thr Cys Ala Gly  
 35 40 45

Thr Thr Gly Thr Cys Cys Ala Ala Cys Cys Cys Cys Gly Gly Ala Ala  
 50 55 60

Ala Cys Gly Gly Gly Ala Ala Ala Ala Ala Gly Cys Ala Ala Gly Thr  
 65 70 75 80

## A-743 PCT.ST25.txt

Thr Thr Thr Cys Cys Cys Cys Gly Cys Thr Cys Cys Cys Gly Gly Cys  
 85 90 95

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 100 105 110

Ala Cys Cys Ala Thr Ala Cys Thr Ala Thr Thr Thr Cys Ala Cys Ala  
 115 120 125

Gly Thr Thr Thr Ala Ala Ala Thr Cys Ala Cys Ala Thr Thr Ala Ala  
 130 135 140

Ala Cys Gly Ala Cys Ala Gly Thr Ala Ala Thr Cys Cys Cys Cys Gly  
 145 150 155 160

Thr Thr Gly Ala Thr Thr Thr Gly Thr Gly Cys Gly Cys Cys Ala Ala  
 165 170 175

Cys Ala Cys Ala Gly Ala Thr Cys Thr Thr Cys Gly Thr Cys Ala Cys  
 180 185 190

Ala Ala Thr Thr Cys Thr Cys Ala Ala Gly Thr Cys Gly Cys Thr Gly  
 195 200 205

Ala Thr Thr Thr Cys Ala Ala Ala Ala Ala Cys Thr Gly Thr Ala  
 210 215 220

Gly Thr Ala Thr Cys Cys Thr Cys Thr Gly Cys Gly Ala Ala Ala Cys  
 225 230 235 240

Gly Ala Thr Cys Cys Cys Thr Gly Thr Thr Thr Gly Ala Gly Thr Ala  
 245 250 255

Thr Thr Gly Ala Gly Gly Ala Gly Gly Cys Gly Ala Gly Ala Thr Gly  
 260 265 270

Thr Cys Gly Cys Ala Gly Ala Cys Ala Gly Ala Ala Ala Thr Gly  
 275 280 285

Cys Ala Gly Thr Gly Ala Cys Thr Thr Cys Cys Thr Cys Ala Thr Thr  
 290 295 300

Gly Ala Gly Thr Cys Ala Ala Ala Ala Gly Cys Gly Gly Thr Thr Thr  
 305 310 315 320

Gly Thr Gly Cys Gly Cys Ala Gly Ala Gly Gly Thr Ala Ala Gly Cys  
 325 330 335

Cys Thr Ala Thr Gly Ala Cys Thr Gly Ala Cys Thr Cys Thr Gly Ala  
 340 345 350

## A-743 PCT.ST25.txt

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 Gly Thr Thr Gly Cys Ala Ala Gly Ala Ala Ala Ala Cys Gly Thr Cys  
 370 375 380  
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 385 390 395 400  
 Ala Ala Ala Ala Gly Thr Thr Thr Thr Thr Gly Thr Cys Ala Ala Ala  
 405 410 415  
 Ala Ala Thr Cys Cys Thr Cys Thr Gly Ala Ala Gly Gly Ala Thr Cys  
 420 425 430  
 Thr Cys Ala Thr Gly Gly Thr Thr Gly Ala Gly Thr Ala Cys Thr Gly  
 435 440 445  
 Cys Gly Ala Gly Ala Gly Ala Gly Ala Gly Gly Gly Ala Thr Ala  
 450 455 460  
 Ala Cys Ala Cys Ala Gly Gly Cys Thr Cys Ala Gly Thr Thr Cys Gly  
 465 470 475 480  
 Thr Thr Gly Ala Gly Ala Ala Ala Ala Thr Cys Ala Thr Cys Ala Ala  
 485 490 495  
 Ala Gly Ala Thr Gly Ala Ala Cys Thr Gly Cys Ala Ala Ala Gly Ala  
 500 505 510  
 Cys Thr Gly Gly Ala Thr Ala Thr Ala Cys Thr Ala Ala Ala Gly Thr  
 515 520 525  
 Ala Ala Ala Gly Ala Cys Thr Thr Thr Ala Cys Thr Thr Thr Gly Thr  
 530 535 540  
 Gly Gly Cys Gly Thr Ala Gly Cys Ala Thr Gly Cys Thr Ala Gly Ala  
 545 550 555 560  
 Thr Thr Ala Cys Thr Gly Ala Thr Cys Gly Thr Thr Thr Ala Ala Gly  
 565 570 575  
 Gly Ala Ala Thr Thr Thr Thr Gly Thr Gly Gly Cys Thr Gly Gly Cys  
 580 585 590  
 Cys Ala Cys Gly Cys Cys Gly Thr Ala Ala Gly Gly Thr Gly Gly Cys  
 595 600 605  
 Ala Ala Gly Gly Ala Ala Cys Thr Gly Gly Thr Thr Cys Thr Gly Ala  
 610 615 620



## A-743 PCT.ST25.txt

Thr Gly Thr Gly Gly Ala Thr Thr Thr Ala Cys Ala Gly Gly Ala Gly  
 625 630 635 640  
 Cys Cys Ala Gly Ala Ala Ala Gly Cys Ala Ala Ala Ala Ala Cys  
 645 650 655  
 Cys Cys Cys Gly Ala Thr Ala Ala Thr Cys Thr Thr Cys Thr Thr Cys  
 660 665 670  
 Ala Ala Cys Thr Thr Thr Thr Gly Cys Gly Ala Gly Thr Ala Cys Gly  
 675 680 685  
 Ala Ala Ala Ala Gly Ala Thr Thr Ala Cys Cys Gly Gly Gly Gly Cys  
 690 695 700  
 Cys Cys Ala Cys Thr Thr Ala Ala Ala Cys Cys Gly Thr Ala Thr Ala  
 705 710 715 720  
 Gly Cys Cys Ala Ala Cys Ala Ala Thr Thr Cys Ala Gly Cys Thr Ala  
 725 730 735  
 Thr Gly Cys Gly Gly Gly Gly Ala Gly Thr Ala Thr Ala Gly Thr Thr  
 740 745 750  
 Ala Thr Ala Thr Gly Cys Cys Cys Gly Gly Ala Ala Ala Ala Gly Thr  
 755 760 765  
 Thr Cys Ala Ala Gly Ala Cys Thr Thr Cys Thr Thr Thr Cys Thr Gly  
 770 775 780  
 Thr Gly Cys Thr Cys Gly Cys Thr Cys Cys Thr Thr Cys Thr Gly Cys  
 785 790 795 800  
 Gly Cys Ala Thr Thr Gly Thr Ala Ala Gly Thr Gly Cys Ala Gly Gly  
 805 810 815  
 Ala Thr Gly Gly Thr Gly Thr Gly Ala Cys Thr Gly Ala Thr Cys Thr  
 820 825 830  
 Thr Cys Ala Cys Cys Ala Ala Ala Cys Gly Thr Ala Thr Thr Ala Cys  
 835 840 845  
 Cys Gly Cys Cys Ala Gly Gly Thr Ala Ala Ala Gly Ala Ala Cys Cys  
 850 855 860  
 Cys Gly Ala Ala Thr Cys Cys Gly Gly Thr Gly Thr Thr Thr Ala Cys  
 865 870 875 880  
 Ala Cys Cys Cys Cys Gly Thr Gly Ala Ala Gly Gly Thr Gly Cys Ala  
 885 890 895

A-743 PCT.ST25.txt

Gly Gly Ala Ala Cys Gly Cys Thr Gly Ala Ala Gly Thr Thr Cys Thr  
                   900                                  905                                  910

Gly Cys Gly Ala Ala Ala Ala Ala Cys Thr Gly Ala Thr Gly Gly Ala  
                   915                                  920                                  925

Ala Ala Ala Gly Gly Cys Gly Gly Thr Gly Gly Gly Cys Thr Thr Cys  
                   930                                  935                                  940

Ala Cys Thr Thr Cys Cys Cys Gly Thr Thr Thr Thr Gly Ala Thr Thr  
                   945                                  950                                  955                                  960

Thr Cys Gly Cys Cys Ala Thr Thr Cys Ala Thr Gly Thr Gly Gly Cys  
                                   965                                  970                                  975

Gly Cys Ala Cys Gly Cys Cys Cys Gly Thr Thr Cys Gly Cys Gly Thr  
                   980                                  985                                  990

Gly Ala Thr Cys Thr Gly Cys Gly Thr Cys Gly Cys Cys Gly Thr Ala  
                   995                                  1000                                  1005

Thr Gly Cys Cys Ala Cys Cys Ala Gly Thr Gly Cys Thr Gly Cys  
                   1010                                  1015                                  1020

Gly Thr Cys Gly Thr Cys Gly Gly Gly Cys Thr Ala Thr Thr Gly  
                   1025                                  1030                                  1035

Ala Thr Gly Cys Gly Cys Thr Cys Thr Thr Gly Cys Ala Gly Gly  
                   1040                                  1045                                  1050

Gly Gly Cys Thr Gly Thr Gly Thr Thr Thr Cys Cys Ala Cys Thr  
                   1055                                  1060                                  1065

Ala Thr Gly Ala Cys Cys Cys Gly Cys Thr Gly Gly Cys Cys Ala  
                   1070                                  1075                                  1080

Ala Cys Cys Gly Cys Gly Thr Cys Cys Ala Gly Thr Gly Cys Thr  
                   1085                                  1090                                  1095

Cys Cys Ala Thr Cys Ala Cys Cys Ala Cys Gly Cys Thr Gly Gly  
                   1100                                  1105                                  1110

Cys Cys Ala Thr Thr Gly Ala Gly Thr Gly Cys Gly Gly Ala Cys  
                   1115                                  1120                                  1125

Thr Gly Gly Cys Gly Ala Cys Gly Gly Ala Gly Thr Cys Thr Gly  
                   1130                                  1135                                  1140

Cys Thr Gly Cys Cys Gly Gly Ala Ala Ala Ala Cys Thr Cys Thr  
                   1145                                  1150                                  1155

## A-743 PCT.ST25.txt

Cys Cys Ala Thr Cys Ala Cys Cys Cys Gly Thr Gly Cys Cys Ala  
 1160 1165 1170  
 Cys Cys Cys Gly Thr Gly Cys Cys Cys Thr Gly Ala Cys Gly Thr  
 1175 1180 1185  
 Thr Cys Cys Thr Gly Thr Cys Ala Gly Ala Gly Cys Thr Gly Gly  
 1190 1195 1200  
 Gly Ala Cys Thr Gly Ala Thr Thr Ala Cys Cys Thr Ala Cys Cys  
 1205 1210 1215  
 Ala Gly Ala Cys Gly Gly Ala Ala Thr Ala Thr Gly Ala Cys Cys  
 1220 1225 1230  
 Cys Gly Cys Thr Thr Ala Thr Cys Gly Gly Gly Thr Gly Cys Thr  
 1235 1240 1245  
 Ala Cys Ala Thr Thr Cys Cys Gly Ala Cys Cys Gly Ala Thr Ala  
 1250 1255 1260  
 Thr Cys Ala Cys Gly Thr Thr Cys Ala Cys Ala Thr Cys Thr Gly  
 1265 1270 1275  
 Cys Ala Cys Thr Gly Thr Thr Thr Gly Cys Thr Gly Cys Cys Cys  
 1280 1285 1290  
 Thr Cys Gly Ala Thr Gly Thr Ala Thr Cys Ala Gly Ala Gly Gly  
 1295 1300 1305  
 Ala Gly Gly Cys Ala Gly Thr Gly Gly Cys Cys Gly Cys Cys Gly  
 1310 1315 1320  
 Cys Gly Cys Gly Cys Cys Gly Cys Ala Gly Cys Cys Gly Thr Gly  
 1325 1330 1335  
 Thr Gly Gly Thr Ala Thr Gly Gly Gly Ala Ala Ala Ala Cys Ala  
 1340 1345 1350  
 Ala Ala Cys Ala Ala Cys Gly Cys Ala Ala Ala Ala Ala Gly Cys  
 1355 1360 1365  
 Ala Gly Gly Gly Cys Thr Gly Gly Ala Thr Ala Cys Cys Cys  
 1370 1375 1380  
 Thr Gly Gly Gly Cys Ala Thr Gly Gly Ala Thr Gly Ala Ala Cys  
 1385 1390 1395  
 Thr Gly Ala Thr Ala Gly Cys Gly Ala Ala Ala Gly Cys Cys Thr  
 1400 1405 1410

A-743 PCT.ST25.txt

Gly Gly Cys Gly Thr Thr Thr Thr Gly Thr Thr Cys Gly Thr Gly  
 1415 1420 1425  
 Ala Gly Cys Gly Thr Thr Thr Thr Cys Gly Cys Ala Gly Thr Thr  
 1430 1435 1440  
 Ala Thr Cys Ala Gly Ala Cys Ala Gly Ala Gly Cys Thr Thr Ala  
 1445 1450 1455  
 Ala Gly Thr Cys Cys Cys Gly Thr Gly Gly Ala Ala Thr Ala Ala  
 1460 1465 1470  
 Ala Gly Cys Gly Thr Gly Cys Cys Cys Gly Thr Gly Cys Gly Cys  
 1475 1480 1485  
 Gly Thr Cys Gly Thr Gly Ala Thr Gly Cys Gly Gly Ala Cys Ala  
 1490 1495 1500  
 Gly Gly Gly Ala Ala Cys Gly Thr Cys Ala Gly Gly Ala Thr Ala  
 1505 1510 1515  
 Thr Thr Gly Thr Cys Ala Cys Cys Cys Thr Gly Gly Thr Gly Ala  
 1520 1525 1530  
 Ala Ala Cys Gly Gly Cys Ala Gly Cys Thr Gly Ala Cys Gly Cys  
 1535 1540 1545  
 Gly Cys Gly Ala Ala Ala Thr Cys Gly Cys Gly Gly Ala Ala Gly  
 1550 1555 1560  
 Gly Gly Cys Gly Cys Thr Thr Cys Ala Cys Thr Gly Cys Cys Ala  
 1565 1570 1575  
 Ala Thr Cys Gly Thr Gly Ala Gly Gly Cys Gly Gly Thr Ala Ala  
 1580 1585 1590  
 Ala Ala Cys Gly Cys Gly Ala Ala Gly Thr Thr Gly Ala Gly Cys  
 1595 1600 1605  
 Gly Thr Cys Gly Thr Gly Thr Gly Ala Ala Gly Gly Ala Gly Cys  
 1610 1615 1620  
 Gly Cys Ala Thr Gly Ala Thr Thr Cys Thr Gly Thr Cys Ala Cys  
 1625 1630 1635  
 Gly Thr Ala Ala Cys Cys Gly Thr Ala Ala Thr Thr Ala Cys Ala  
 1640 1645 1650  
 Gly Cys Cys Gly Gly Cys Thr Gly Gly Cys Cys Ala Cys Ala Gly  
 1655 1660 1665

## A-743 PCT.ST25.txt

Cys Thr Thr Cys Cys Cys Cys Cys Thr Gly Ala Ala Ala Gly Thr  
 1670 1675 1680  
 Gly Ala Cys Cys Thr Cys Cys Thr Cys Thr Gly Ala Ala Thr Ala  
 1685 1690 1695  
 Ala Thr Cys Cys Gly Gly Cys Cys Thr Gly Cys Gly Cys Cys Gly  
 1700 1705 1710  
 Gly Ala Gly Gly Cys Thr Thr Cys Cys Gly Cys Ala Cys Gly Thr  
 1715 1720 1725  
 Cys Thr Gly Ala Ala Gly Cys Cys Cys Gly Ala Cys Ala Gly Cys  
 1730 1735 1740  
 Gly Cys Ala Cys Ala Ala Ala Ala Ala Thr Cys Ala Gly Cys  
 1745 1750 1755  
 Ala Cys Cys Ala Cys Ala Thr Ala Cys Ala Ala Ala Ala Ala Ala  
 1760 1765 1770  
 Cys Ala Ala Cys Cys Thr Cys Ala Thr Cys Ala Thr Cys Cys Ala  
 1775 1780 1785  
 Gly Cys Thr Thr Cys Thr Gly Gly Thr Gly Cys Ala Thr Cys Cys  
 1790 1795 1800  
 Gly Gly Cys Cys Cys Cys Cys Cys Cys Thr Gly Thr Thr Thr Thr  
 1805 1810 1815  
 Cys Gly Ala Thr Ala Cys Ala Ala Ala Ala Cys Ala Cys Gly Cys  
 1820 1825 1830  
 Cys Thr Cys Ala Cys Ala Gly Ala Cys Gly Gly Gly Gly Ala Ala  
 1835 1840 1845  
 Thr Thr Thr Thr Gly Cys Thr Thr Ala Thr Cys Cys Ala Cys Ala  
 1850 1855 1860  
 Thr Thr Ala Ala Ala Cys Thr Gly Cys Ala Ala Gly Gly Gly Ala  
 1865 1870 1875  
 Cys Thr Thr Cys Cys Cys Cys Ala Thr Ala Ala Gly Gly Thr Thr  
 1880 1885 1890  
 Ala Cys Ala Ala Cys Cys Gly Thr Thr Cys Ala Thr Gly Thr Cys  
 1895 1900 1905  
 Ala Thr Ala Ala Ala Gly Cys Gly Cys Cys Ala Thr Cys Cys Gly  
 1910 1915 1920

A-743 PCT.ST25.txt

|             |     |     |     |     |     |             |     |     |     |     |             |     |     |     |
|-------------|-----|-----|-----|-----|-----|-------------|-----|-----|-----|-----|-------------|-----|-----|-----|
| Cys<br>1925 | Cys | Ala | Gly | Cys | Gly | Thr<br>1930 | Thr | Ala | Cys | Ala | Gly<br>1935 | Gly | Gly | Thr |
| Gly<br>1940 | Cys | Ala | Ala | Thr | Gly | Thr<br>1945 | Ala | Thr | Cys | Thr | Thr<br>1950 | Thr | Thr | Ala |
| Ala<br>1955 | Ala | Cys | Ala | Cys | Cys | Thr<br>1960 | Gly | Thr | Thr | Thr | Ala<br>1965 | Thr | Ala | Thr |
| Cys<br>1970 | Thr | Cys | Cys | Thr | Thr | Thr<br>1975 | Ala | Ala | Ala | Cys | Thr<br>1980 | Ala | Cys | Thr |
| Thr<br>1985 | Ala | Ala | Thr | Thr | Ala | Cys<br>1990 | Ala | Thr | Thr | Cys | Ala<br>1995 | Thr | Thr | Thr |
| Ala<br>2000 | Ala | Ala | Ala | Ala | Gly | Ala<br>2005 | Ala | Ala | Ala | Cys | Cys<br>2010 | Thr | Ala | Thr |
| Thr<br>2015 | Cys | Ala | Cys | Thr | Gly | Cys<br>2020 | Cys | Thr | Gly | Thr | Cys<br>2025 | Cys | Thr | Thr |
| Gly<br>2030 | Gly | Ala | Cys | Ala | Gly | Ala<br>2035 | Cys | Ala | Gly | Ala | Thr<br>2040 | Ala | Thr | Gly |
| Cys<br>2045 | Ala | Cys | Cys | Thr | Cys | Cys<br>2050 | Cys | Ala | Cys | Cys | Gly<br>2055 | Cys | Ala | Ala |
| Gly<br>2060 | Cys | Gly | Gly | Cys | Gly | Gly<br>2065 | Gly | Cys | Cys | Cys | Cys<br>2070 | Thr | Ala | Cys |
| Cys<br>2075 | Gly | Gly | Ala | Gly | Cys | Cys<br>2080 | Gly | Cys | Thr | Thr | Thr<br>2085 | Ala | Gly | Thr |
| Thr<br>2090 | Ala | Cys | Ala | Ala | Cys | Ala<br>2095 | Cys | Thr | Cys | Ala | Gly<br>2100 | Ala | Cys | Ala |
| Cys<br>2105 | Ala | Ala | Cys | Cys | Ala | Cys<br>2110 | Cys | Ala | Gly | Ala | Ala<br>2115 | Ala | Ala | Ala |
| Cys<br>2120 | Cys | Cys | Cys | Gly | Gly | Thr<br>2125 | Cys | Cys | Ala | Gly | Cys<br>2130 | Gly | Cys | Ala |
| Gly<br>2135 | Ala | Ala | Cys | Thr | Gly | Ala<br>2140 | Ala | Ala | Cys | Cys | Ala<br>2145 | Cys | Ala | Ala |
| Ala<br>2150 | Gly | Cys | Cys | Cys | Cys | Thr<br>2155 | Cys | Cys | Cys | Thr | Cys<br>2160 | Ala | Thr | Ala |
| Ala<br>2165 | Cys | Thr | Gly | Ala | Ala | Ala<br>2170 | Ala | Gly | Cys | Gly | Gly<br>2175 | Cys | Cys | Cys |

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Cys Gly Cys Cys Cys Cys Gly Gly Thr Cys Cys Gly Ala Ala Gly  
 2180 2185 2190  
 Gly Gly Cys Cys Gly Gly Ala Ala Cys Ala Gly Ala Gly Thr Cys  
 2195 2200 2205  
 Gly Cys Thr Thr Thr Thr Ala Ala Thr Thr Ala Thr Gly Ala Ala  
 2210 2215 2220  
 Thr Gly Thr Thr Gly Thr Ala Ala Cys Thr Ala Cys Thr Thr Cys  
 2225 2230 2235  
 Ala Thr Cys Ala Thr Cys Gly Cys Thr Gly Thr Cys Ala Gly Thr  
 2240 2245 2250  
 Cys Thr Thr Cys Thr Cys Gly Cys Thr Gly Gly Ala Ala Gly Thr  
 2255 2260 2265  
 Thr Cys Thr Cys Ala Gly Thr Ala Cys Ala Cys Gly Cys Thr Cys  
 2270 2275 2280  
 Gly Thr Ala Ala Gly Cys Gly Gly Cys Cys Cys Thr Gly Ala Cys  
 2285 2290 2295  
 Gly Gly Cys Cys Cys Gly Cys Thr Ala Ala Cys Gly Cys Gly Gly  
 2300 2305 2310  
 Ala Gly Ala Thr Ala Cys Gly Cys Cys Cys Cys Gly Ala Cys Thr  
 2315 2320 2325  
 Thr Cys Gly Gly Gly Thr Ala Ala Ala Cys Cys Cys Thr Cys Gly  
 2330 2335 2340  
 Thr Cys Gly Gly Gly Ala Cys Cys Ala Cys Thr Cys Cys Gly Ala  
 2345 2350 2355  
 Cys Cys Gly Cys Gly Cys Ala Cys Ala Gly Ala Ala Gly Cys Thr  
 2360 2365 2370  
 Cys Thr Cys Thr Cys Ala Thr Gly Gly Cys Thr Gly Ala Ala Ala  
 2375 2380 2385  
 Gly Cys Gly Gly Gly Thr Ala Thr Gly Gly Thr Cys Thr Gly Gly  
 2390 2395 2400  
 Cys Ala Gly Gly Gly Cys Thr Gly Gly Gly Gly Ala Thr Gly Gly  
 2405 2410 2415  
 Gly Thr Ala Ala Gly Gly Thr Gly Ala Ala Ala Thr Cys Thr Ala  
 2420 2425 2430

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Thr Cys Ala Ala Thr Cys Ala Gly Thr Ala Cys Cys Gly Gly Cys  
 2435 2440 2445  
 Thr Thr Ala Cys Gly Cys Cys Gly Gly Gly Cys Thr Thr Cys Gly  
 2450 2455 2460  
 Gly Cys Gly Gly Thr Thr Thr Thr Ala Cys Thr Cys Cys Thr Gly  
 2465 2470 2475  
 Thr Thr Thr Cys Ala Thr Ala Thr Ala Thr Gly Ala Ala Ala Cys  
 2480 2485 2490  
 Ala Ala Cys Ala Gly Gly Thr Cys Ala Cys Cys Gly Cys Cys Thr  
 2495 2500 2505  
 Thr Cys Cys Ala Thr Gly Cys Cys Gly Cys Thr Gly Ala Thr Gly  
 2510 2515 2520  
 Cys Gly Gly Cys Ala Thr Ala Thr Cys Cys Thr Gly Gly Thr Ala  
 2525 2530 2535  
 Ala Cys Gly Ala Thr Ala Thr Cys Thr Gly Ala Ala Thr Thr Gly  
 2540 2545 2550  
 Thr Thr Ala Thr Ala Cys Ala Thr Gly Thr Gly Thr Ala Thr Ala  
 2555 2560 2565  
 Thr Ala Cys Gly Thr Gly Gly Thr Ala Ala Thr Gly Ala Cys Ala  
 2570 2575 2580  
 Ala Ala Ala Ala Thr Ala Gly Gly Ala Cys Ala Ala Gly Thr Thr  
 2585 2590 2595  
 Ala Ala Ala Ala Ala Thr Thr Thr Ala Cys Ala Gly Gly Cys Gly  
 2600 2605 2610  
 Ala Thr Gly Cys Ala Ala Thr Gly Ala Thr Thr Cys Ala Ala Ala  
 2615 2620 2625  
 Cys Ala Cys Gly Thr Ala Ala Thr Cys Ala Ala Thr Ala Thr Cys  
 2630 2635 2640  
 Gly Gly Gly Gly Gly Thr Gly Gly Gly Cys Gly Ala Ala Gly Ala  
 2645 2650 2655  
 Ala Cys Thr Cys Cys Ala Gly Cys Ala Thr Gly Ala Gly Ala Thr  
 2660 2665 2670  
 Cys Cys Cys Cys Gly Cys Gly Cys Thr Gly Gly Ala Gly Gly Ala  
 2675 2680 2685



## A-743 PCT.ST25.txt

Thr Cys Ala Thr Cys Cys Ala Gly Cys Cys Gly Gly Cys Gly Thr  
 2690 2695 2700  
 Cys Cys Cys Gly Gly Ala Ala Ala Ala Cys Gly Ala Thr Thr Cys  
 2705 2710 2715  
 Cys Gly Ala Ala Gly Cys Cys Cys Ala Ala Cys Cys Thr Thr Thr  
 2720 2725 2730  
 Cys Ala Thr Ala Gly Ala Ala Gly Gly Cys Gly Gly Cys Gly Gly  
 2735 2740 2745  
 Thr Gly Gly Ala Ala Thr Cys Gly Ala Ala Ala Thr Cys Thr Cys  
 2750 2755 2760  
 Gly Thr Gly Ala Thr Gly Gly Cys Ala Gly Gly Thr Thr Gly Gly  
 2765 2770 2775  
 Gly Cys Gly Thr Cys Gly Cys Thr Thr Gly Gly Thr Cys Gly Gly  
 2780 2785 2790  
 Thr Cys Ala Thr Thr Thr Cys Gly Ala Ala Cys Cys Cys Cys Ala  
 2795 2800 2805  
 Gly Ala Gly Thr Cys Cys Cys Gly Cys Thr Cys Ala Gly Ala Ala  
 2810 2815 2820  
 Gly Ala Ala Cys Thr Cys Gly Thr Cys Ala Ala Gly Ala Ala Gly  
 2825 2830 2835  
 Gly Cys Gly Ala Thr Ala Gly Ala Ala Gly Gly Cys Gly Ala Thr  
 2840 2845 2850  
 Gly Cys Gly Cys Thr Gly Cys Gly Ala Ala Thr Cys Gly Gly Gly  
 2855 2860 2865  
 Ala Gly Cys Gly Gly Cys Gly Ala Thr Ala Cys Cys Gly Thr Ala  
 2870 2875 2880  
 Ala Ala Gly Cys Ala Cys Gly Ala Gly Gly Ala Ala Gly Cys Gly  
 2885 2890 2895  
 Gly Thr Cys Ala Gly Cys Cys Cys Ala Thr Thr Cys Gly Cys Cys  
 2900 2905 2910  
 Gly Cys Cys Ala Ala Gly Cys Thr Cys Thr Thr Cys Ala Gly Cys  
 2915 2920 2925  
 Ala Ala Thr Ala Thr Cys Ala Cys Gly Gly Gly Thr Ala Gly Cys  
 2930 2935 2940

A-743 PCT.ST25.txt

Cys Ala Ala Cys Gly Cys Thr Ala Thr Gly Thr Cys Cys Thr Gly  
 2945 2950 2955  
 Ala Thr Ala Gly Cys Gly Gly Thr Cys Cys Gly Cys Cys Ala Cys  
 2960 2965 2970  
 Ala Cys Cys Cys Ala Gly Cys Cys Gly Gly Cys Cys Ala Cys Ala  
 2975 2980 2985  
 Gly Thr Cys Gly Ala Thr Gly Ala Ala Thr Cys Cys Ala Gly Ala  
 2990 2995 3000  
 Ala Ala Ala Gly Cys Gly Gly Cys Cys Ala Thr Thr Thr Thr Cys  
 3005 3010 3015  
 Cys Ala Cys Cys Ala Thr Gly Ala Thr Ala Thr Thr Cys Gly Gly  
 3020 3025 3030  
 Cys Ala Ala Gly Cys Ala Gly Gly Cys Ala Thr Cys Gly Cys Cys  
 3035 3040 3045  
 Ala Thr Gly Ala Gly Thr Cys Ala Cys Gly Ala Cys Gly Ala Gly  
 3050 3055 3060  
 Ala Thr Cys Cys Thr Cys Gly Cys Cys Gly Thr Cys Gly Gly Gly  
 3065 3070 3075  
 Cys Ala Thr Gly Cys Gly Cys Gly Cys Cys Thr Thr Gly Ala Gly  
 3080 3085 3090  
 Cys Cys Thr Gly Gly Cys Gly Ala Ala Cys Ala Gly Thr Thr Cys  
 3095 3100 3105  
 Gly Gly Cys Thr Gly Gly Cys Gly Cys Gly Ala Gly Cys Cys Cys  
 3110 3115 3120  
 Cys Thr Gly Ala Thr Gly Cys Thr Cys Thr Thr Cys Gly Thr Cys  
 3125 3130 3135  
 Cys Ala Gly Ala Thr Cys Ala Thr Cys Cys Thr Gly Ala Thr Cys  
 3140 3145 3150  
 Gly Ala Cys Ala Ala Gly Ala Cys Cys Gly Gly Cys Thr Thr Cys  
 3155 3160 3165  
 Cys Ala Thr Cys Cys Gly Ala Gly Thr Ala Cys Gly Thr Gly Cys  
 3170 3175 3180  
 Thr Cys Gly Cys Thr Cys Gly Ala Thr Gly Cys Gly Ala Thr Gly  
 3185 3190 3195

## A-743 PCT.ST25.txt

Thr Thr Thr Cys Gly Cys Thr Thr Gly Gly Thr Gly Gly Thr Cys  
 3200 3205 3210  
 Gly Ala Ala Thr Gly Gly Gly Cys Ala Gly Gly Thr Ala Gly Cys  
 3215 3220 3225  
 Cys Gly Gly Ala Thr Cys Ala Ala Gly Cys Gly Thr Ala Thr Gly  
 3230 3235 3240  
 Cys Ala Gly Cys Cys Gly Cys Cys Gly Cys Ala Thr Thr Gly Cys  
 3245 3250 3255  
 Ala Thr Cys Ala Gly Cys Cys Ala Thr Gly Ala Thr Gly Gly Ala  
 3260 3265 3270  
 Thr Ala Cys Thr Thr Thr Cys Thr Cys Gly Gly Cys Ala Gly Gly  
 3275 3280 3285  
 Ala Gly Cys Ala Ala Gly Gly Thr Gly Ala Gly Ala Thr Gly Ala  
 3290 3295 3300  
 Cys Ala Gly Gly Ala Gly Ala Thr Cys Cys Thr Gly Cys Cys Cys  
 3305 3310 3315  
 Cys Gly Gly Cys Ala Cys Thr Thr Cys Gly Cys Cys Cys Ala Ala  
 3320 3325 3330  
 Thr Ala Gly Cys Ala Gly Cys Cys Ala Gly Thr Cys Cys Cys Thr  
 3335 3340 3345  
 Thr Cys Cys Cys Gly Cys Thr Thr Cys Ala Gly Thr Gly Ala Cys  
 3350 3355 3360  
 Ala Ala Cys Gly Thr Cys Gly Ala Gly Cys Ala Cys Ala Gly Cys  
 3365 3370 3375  
 Thr Gly Cys Gly Cys Ala Ala Gly Gly Ala Ala Cys Gly Cys Cys  
 3380 3385 3390  
 Cys Gly Thr Cys Gly Thr Gly Gly Cys Cys Ala Gly Cys Cys Ala  
 3395 3400 3405  
 Cys Gly Ala Thr Ala Gly Cys Cys Gly Cys Gly Cys Thr Gly Cys  
 3410 3415 3420  
 Cys Thr Cys Gly Thr Cys Cys Thr Gly Cys Ala Ala Thr Thr Cys  
 3425 3430 3435  
 Ala Thr Thr Cys Ala Gly Gly Ala Cys Ala Cys Cys Gly Gly Ala  
 3440 3445 3450

A-743 PCT.ST25.txt

Cys Ala Gly Gly Thr Cys Gly Gly Thr Cys Thr Thr Gly Ala Cys  
 3455 3460 3465  
 Ala Ala Ala Ala Ala Gly Ala Ala Cys Cys Gly Gly Gly Cys Gly  
 3470 3475 3480  
 Cys Cys Cys Cys Thr Gly Cys Gly Cys Thr Gly Ala Cys Ala Gly  
 3485 3490 3495  
 Cys Cys Gly Gly Ala Ala Cys Ala Cys Gly Gly Cys Gly Gly Cys  
 3500 3505 3510  
 Ala Thr Cys Ala Gly Ala Gly Cys Ala Gly Cys Cys Gly Ala Thr  
 3515 3520 3525  
 Thr Gly Thr Cys Thr Gly Thr Thr Gly Thr Gly Cys Cys Cys Ala  
 3530 3535 3540  
 Gly Thr Cys Ala Thr Ala Gly Cys Cys Gly Ala Ala Thr Ala Gly  
 3545 3550 3555  
 Cys Cys Thr Cys Thr Cys Cys Ala Cys Cys Cys Ala Ala Gly Cys  
 3560 3565 3570  
 Gly Gly Cys Cys Gly Gly Ala Gly Ala Ala Cys Cys Thr Gly Cys  
 3575 3580 3585  
 Gly Thr Gly Cys Ala Ala Thr Cys Cys Ala Thr Cys Thr Thr Gly  
 3590 3595 3600  
 Thr Thr Cys Ala Ala Thr Cys Ala Thr Gly Cys Gly Ala Ala Ala  
 3605 3610 3615  
 Cys Gly Ala Thr Cys Cys Thr Cys Ala Thr Cys Cys Thr Gly Thr  
 3620 3625 3630  
 Cys Thr Cys Thr Thr Gly Ala Thr Cys Thr Gly Ala Thr Cys Thr  
 3635 3640 3645  
 Thr Gly Ala Thr Cys Cys Cys Cys Thr Gly Cys Gly Cys Cys Ala  
 3650 3655 3660  
 Thr Cys Ala Gly Ala Thr Cys Cys Thr Thr Gly Gly Cys Gly Gly  
 3665 3670 3675  
 Cys Ala Ala Gly Ala Ala Ala Gly Cys Cys Ala Thr Cys Cys Ala  
 3680 3685 3690  
 Gly Thr Thr Thr Ala Cys Thr Thr Thr Gly Cys Ala Gly Gly Gly  
 3695 3700 3705

## A-743 PCT.ST25.txt

Cys Thr Thr Cys Cys Cys Ala Ala Cys Cys Thr Thr Ala Cys Cys  
 3710 3715 3720  
 Ala Gly Ala Gly Gly Gly Cys Gly Cys Cys Cys Cys Ala Gly Cys  
 3725 3730 3735  
 Thr Gly Gly Cys Ala Ala Thr Thr Cys Cys Gly Gly Thr Thr Cys  
 3740 3745 3750  
 Gly Cys Thr Thr Gly Cys Thr Gly Thr Cys Cys Ala Thr Ala Ala  
 3755 3760 3765  
 Ala Ala Cys Cys Gly Cys Cys Cys Ala Gly Thr Cys Thr Ala Gly  
 3770 3775 3780  
 Cys Thr Ala Thr Cys Gly Cys Cys Ala Thr Gly Thr Ala Ala Gly  
 3785 3790 3795  
 Cys Cys Cys Ala Cys Thr Gly Cys Ala Ala Gly Cys Thr Ala Cys  
 3800 3805 3810  
 Cys Thr Gly Cys Thr Thr Thr Cys Thr Cys Thr Thr Thr Gly Cys  
 3815 3820 3825  
 Gly Cys Thr Thr Gly Cys Gly Thr Thr Thr Thr Cys Cys Cys Thr  
 3830 3835 3840  
 Thr Gly Thr Cys Cys Ala Gly Ala Thr Ala Gly Cys Cys Cys Ala  
 3845 3850 3855  
 Gly Thr Ala Gly Cys Thr Gly Ala Cys Ala Thr Thr Cys Ala Thr  
 3860 3865 3870  
 Cys Cys Gly Gly Gly Gly Thr Cys Ala Gly Cys Ala Cys Cys Gly  
 3875 3880 3885  
 Thr Thr Thr Cys Thr Gly Cys Gly Gly Ala Cys Thr Gly Gly Cys  
 3890 3895 3900  
 Thr Thr Thr Cys Thr Ala Cys Gly Thr Gly Thr Thr Cys Cys Gly  
 3905 3910 3915  
 Cys Thr Thr Cys Cys Thr Thr Thr Ala Gly Cys Ala Gly Cys Cys  
 3920 3925 3930  
 Cys Thr Thr Gly Cys Gly Cys Cys Cys Thr Gly Ala Gly Thr Gly  
 3935 3940 3945  
 Cys Thr Thr Gly Cys Gly Gly Cys Ala Gly Cys Gly Thr Gly Ala  
 3950 3955 3960

A-743 PCT.ST25.txt

Ala Gly Cys Thr Ala Cys Ala Thr Ala Thr Ala Thr Gly Thr Gly  
3965 3970 3975

Ala Thr Cys Cys Gly Gly Gly Cys Ala Ala Ala Thr Cys Gly Cys  
3980 3985 3990

Thr Gly Ala Ala Thr Ala Thr Thr Cys Cys Thr Thr Thr Thr Gly  
3995 4000 4005

Thr Cys Thr Cys Cys Gly Ala Cys Cys Ala Thr Cys Ala Gly Gly  
4010 4015 4020

Cys Ala Cys Cys Thr Gly Ala Gly Thr Cys Gly Cys Thr Gly Thr  
4025 4030 4035

Cys Thr Thr Thr Thr Thr Cys Gly Thr Gly Ala Cys Ala Thr Thr  
4040 4045 4050

Cys Ala Gly Thr Thr Cys Gly Cys Thr Gly Cys Gly Cys Thr Cys  
4055 4060 4065

Ala Cys Gly Gly Cys Thr Cys Thr Gly Gly Cys Ala Gly Thr Gly  
4070 4075 4080

Ala Ala Thr Gly Gly Gly Gly Gly Thr Ala Ala Ala Thr Gly Gly  
4085 4090 4095

Cys Ala Cys Thr Ala Cys Ala Gly Gly Cys Gly Cys Cys Thr Thr  
4100 4105 4110

Thr Thr Ala Thr Gly Gly Ala Thr Thr Cys Ala Thr Gly Cys Ala  
4115 4120 4125

Ala Gly Gly Ala Ala Ala Cys Thr Ala Cys Cys Cys Ala Thr Ala  
4130 4135 4140

Ala Thr Ala Cys Ala Ala Gly Ala Ala Ala Ala Gly Cys Cys Cys  
4145 4150 4155

Gly Thr Cys Ala Cys Gly Gly Gly Cys Thr Thr Cys Thr Cys Ala  
4160 4165 4170

Gly Gly Gly Cys Gly Thr Thr Thr Thr Ala Thr Gly Gly Cys Gly  
4175 4180 4185

Gly Gly Thr Cys Thr Gly Cys Thr Ala Thr Gly Thr Gly Gly Thr  
4190 4195 4200

Gly Cys Thr Ala Thr Cys Thr Gly Ala Cys Thr Thr Thr Thr Thr  
4205 4210 4215

## A-743 PCT.ST25.txt

Gly Cys Thr Gly Thr Thr Cys Ala Gly Cys Ala Gly Thr Thr Cys  
 4220 4225 4230  
 Cys Thr Gly Cys Cys Cys Thr Cys Thr Gly Ala Thr Thr Thr Thr  
 4235 4240 4245  
 Cys Cys Ala Gly Thr Cys Thr Gly Ala Cys Cys Ala Cys Thr Thr  
 4250 4255 4260  
 Cys Gly Gly Ala Thr Thr Ala Thr Cys Cys Cys Gly Thr Gly Ala  
 4265 4270 4275  
 Cys Ala Gly Gly Thr Cys Ala Thr Thr Cys Ala Gly Ala Cys Thr  
 4280 4285 4290  
 Gly Gly Cys Thr Ala Ala Thr Gly Cys Ala Cys Cys Cys Ala Gly  
 4295 4300 4305  
 Thr Ala Ala Gly Gly Cys Ala Gly Cys Gly Gly Thr Ala Thr Cys  
 4310 4315 4320  
 Ala Thr Cys Ala Ala Cys Ala Gly Gly Cys Thr Thr Ala Cys Cys  
 4325 4330 4335  
 Cys Gly Thr Cys Thr Thr Ala Cys Thr Gly Thr Cys Gly Ala Ala  
 4340 4345 4350  
 Gly Ala Cys Gly Thr Gly Cys Gly Thr Ala Ala Cys Gly Thr Ala  
 4355 4360 4365  
 Thr Gly Cys Ala Thr Gly Gly Thr Cys Thr Cys Cys Cys Cys Ala  
 4370 4375 4380  
 Thr Gly Cys Gly Ala Gly Ala Gly Thr Ala Gly Gly Gly Ala Ala  
 4385 4390 4395  
 Cys Thr Gly Cys Cys Ala Gly Gly Cys Ala Thr Cys Ala Ala Ala  
 4400 4405 4410  
 Thr Ala Ala Ala Ala Cys Gly Ala Ala Ala Gly Gly Cys Thr Cys  
 4415 4420 4425  
 Ala Gly Thr Cys Gly Ala Ala Ala Gly Ala Cys Thr Gly Gly Gly  
 4430 4435 4440  
 Cys Cys Thr Thr Thr Cys Gly Thr Thr Thr Thr Ala Thr Cys Thr  
 4445 4450 4455  
 Gly Thr Thr Gly Thr Thr Thr Gly Thr Cys Gly Gly Thr Gly Ala  
 4460 4465 4470

## A-743 PCT.ST25.txt

Ala Cys Gly Cys Thr Cys Thr Cys Cys Thr Gly Ala Gly Thr Ala  
 4475 4480 4485  
 Gly Gly Ala Cys Ala Ala Ala Thr Cys Cys Gly Cys Cys Gly Gly  
 4490 4495 4500  
 Gly Ala Gly Cys Gly Gly Ala Thr Thr Thr Gly Ala Ala Cys Gly  
 4505 4510 4515  
 Thr Thr Gly Cys Gly Ala Ala Gly Cys Ala Ala Cys Gly Gly Cys  
 4520 4525 4530  
 Cys Cys Gly Gly Ala Gly Gly Gly Thr Gly Gly Cys Gly Gly Gly  
 4535 4540 4545  
 Cys Ala Gly Gly Ala Cys Gly Cys Cys Cys Gly Cys Cys Ala Thr  
 4550 4555 4560  
 Ala Ala Ala Cys Thr Gly Cys Cys Ala Gly Gly Cys Ala Thr Cys  
 4565 4570 4575  
 Ala Ala Ala Thr Thr Ala Ala Gly Cys Ala Gly Ala Ala Gly Gly  
 4580 4585 4590  
 Cys Cys Ala Thr Cys Cys Thr Gly Ala Cys Gly Gly Ala Thr Gly  
 4595 4600 4605  
 Gly Cys Cys Thr Thr Thr Thr Thr Gly Cys Gly Thr Thr Thr Cys  
 4610 4615 4620  
 Thr Ala Cys Ala Ala Ala Cys Thr Cys Thr Thr Thr Thr Gly Thr  
 4625 4630 4635  
 Thr Thr Ala Thr Thr Thr Thr Thr Cys Thr Ala Ala Ala Thr Ala  
 4640 4645 4650  
 Cys Ala Thr Thr Cys Ala Ala Ala Thr Ala Thr Gly Gly Ala Cys  
 4655 4660 4665  
 Gly Thr Cys Gly Thr Ala Cys Thr Thr Ala Ala Cys Thr Thr Thr  
 4670 4675 4680  
 Thr Ala Ala Ala Gly Thr Ala Thr Gly Gly Gly Cys Ala Ala Thr  
 4685 4690 4695  
 Cys Ala Ala Thr Thr Gly Cys Thr Cys Cys Thr Gly Thr Thr Ala  
 4700 4705 4710  
 Ala Ala Ala Thr Thr Gly Cys Thr Thr Thr Ala Gly Ala Ala Ala  
 4715 4720 4725



## A-743 PCT.ST25.txt

Thr Ala Cys Thr Thr Thr Gly Gly Cys Ala Gly Cys Gly Gly Thr  
 4730 4735 4740  
 Thr Thr Gly Thr Thr Gly Thr Ala Thr Thr Gly Ala Gly Thr Thr  
 4745 4750 4755  
 Thr Cys Ala Thr Thr Thr Gly Cys Gly Cys Ala Thr Thr Gly Gly  
 4760 4765 4770  
 Thr Thr Ala Ala Ala Thr Gly Gly Ala Ala Ala Gly Thr Gly Ala  
 4775 4780 4785  
 Cys Cys Gly Thr Gly Cys Gly Cys Thr Thr Ala Cys Thr Ala Cys  
 4790 4795 4800  
 Ala Gly Cys Cys Thr Ala Ala Thr Ala Thr Thr Thr Thr Thr Gly  
 4805 4810 4815  
 Ala Ala Ala Thr Ala Thr Cys Cys Cys Ala Ala Gly Ala Gly Cys  
 4820 4825 4830  
 Thr Thr Thr Thr Thr Cys Cys Thr Thr Cys Gly Cys Ala Thr Gly  
 4835 4840 4845  
 Cys Cys Cys Ala Cys Gly Cys Thr Ala Ala Ala Cys Ala Thr Thr  
 4850 4855 4860  
 Cys Thr Thr Thr Thr Thr Cys Thr Cys Thr Thr Thr Thr Gly Gly  
 4865 4870 4875  
 Thr Thr Ala Ala Ala Thr Cys Gly Thr Thr Gly Thr Thr Thr Gly  
 4880 4885 4890  
 Ala Thr Thr Thr Ala Thr Thr Ala Thr Thr Thr Gly Cys Thr Ala  
 4895 4900 4905  
 Thr Ala Thr Thr Thr Ala Thr Thr Thr Thr Thr Cys Gly Ala Thr  
 4910 4915 4920  
 Ala Ala Thr Thr Ala Thr Cys Ala Ala Cys Thr Ala Gly Ala Gly  
 4925 4930 4935  
 Ala Ala Gly Gly Ala Ala Cys Ala Ala Thr Thr Ala Ala Thr Gly  
 4940 4945 4950  
 Gly Thr Ala Thr Gly Thr Thr Cys Ala Thr Ala Cys Ala Cys Gly  
 4955 4960 4965  
 Cys Ala Thr Gly Thr Ala Ala Ala Ala Thr Ala Ala Ala Cys  
 4970 4975 4980

## A-743 PCT.ST25.txt

Thr Ala Thr Cys Thr Ala Thr Ala Thr Ala Gly Thr Thr Gly Thr  
 4985 4990 4995  
 Cys Thr Thr Thr Cys Thr Cys Thr Gly Ala Ala Thr Gly Thr Gly  
 5000 5005 5010  
 Cys Ala Ala Ala Ala Cys Thr Ala Ala Gly Cys Ala Thr Thr Cys  
 5015 5020 5025  
 Cys Gly Ala Ala Gly Cys Cys Ala Thr Thr Ala Thr Thr Ala Gly  
 5030 5035 5040  
 Cys Ala Gly Thr Ala Thr Gly Ala Ala Thr Ala Gly Gly Gly Ala  
 5045 5050 5055  
 Ala Ala Cys Thr Ala Ala Ala Cys Cys Cys Ala Gly Thr Gly Ala  
 5060 5065 5070  
 Thr Ala Ala Gly Ala Cys Cys Thr Gly Ala Thr Gly Ala Thr Thr  
 5075 5080 5085  
 Thr Cys Gly Cys Thr Thr Cys Thr Thr Thr Ala Ala Thr Thr Ala  
 5090 5095 5100  
 Cys Ala Thr Thr Thr Gly Gly Ala Gly Ala Thr Thr Thr Thr Thr  
 5105 5110 5115  
 Thr Ala Thr Thr Thr Ala Cys Ala Gly Cys Ala Thr Thr Gly Thr  
 5120 5125 5130  
 Thr Thr Thr Cys Ala Ala Ala Thr Ala Thr Ala Thr Thr Cys Cys  
 5135 5140 5145  
 Ala Ala Thr Thr Ala Ala Thr Cys Gly Gly Thr Gly Ala Ala Thr  
 5150 5155 5160  
 Gly Ala Thr Thr Gly Gly Ala Gly Thr Thr Ala Gly Ala Ala Thr  
 5165 5170 5175  
 Ala Ala Thr Cys Thr Ala Cys Thr Ala Thr Ala Gly Gly Ala Thr  
 5180 5185 5190  
 Cys Ala Thr Ala Thr Thr Thr Thr Ala Thr Thr Ala Ala Ala Thr  
 5195 5200 5205  
 Thr Ala Gly Cys Gly Thr Cys Ala Thr Cys Ala Thr Ala Ala Thr  
 5210 5215 5220  
 Ala Thr Thr Gly Cys Cys Thr Cys Cys Ala Thr Thr Thr Thr Thr  
 5225 5230 5235

## A-743 PCT.ST25.txt

Thr Ala Gly Gly Gly Thr Ala Ala Thr Thr Ala Thr Cys Cys Ala  
 5240 5245 5250  
 Gly Ala Ala Thr Thr Gly Ala Ala Ala Thr Ala Thr Cys Ala Gly  
 5255 5260 5265  
 Ala Thr Thr Thr Ala Ala Cys Cys Ala Thr Ala Gly Ala Ala Thr  
 5270 5275 5280  
 Gly Ala Gly Gly Ala Thr Ala Ala Ala Thr Gly Ala Thr Cys Gly  
 5285 5290 5295  
 Cys Gly Ala Gly Thr Ala Ala Ala Thr Ala Ala Thr Ala Thr Thr  
 5300 5305 5310  
 Cys Ala Cys Ala Ala Thr Gly Thr Ala Cys Cys Ala Thr Thr Thr  
 5315 5320 5325  
 Thr Ala Gly Thr Cys Ala Thr Ala Thr Cys Ala Gly Ala Thr Ala  
 5330 5335 5340  
 Ala Gly Cys Ala Thr Thr Gly Ala Thr Thr Ala Ala Thr Ala Thr  
 5345 5350 5355  
 Cys Ala Thr Thr Ala Thr Thr Gly Cys Thr Thr Cys Thr Ala Cys  
 5360 5365 5370  
 Ala Gly Gly Cys Thr Thr Thr Ala Ala Thr Thr Thr Thr Ala Thr  
 5375 5380 5385  
 Thr Ala Ala Thr Thr Ala Thr Thr Cys Thr Gly Thr Ala Ala Gly  
 5390 5395 5400  
 Thr Gly Thr Cys Gly Thr Cys Gly Gly Cys Ala Thr Thr Thr Ala  
 5405 5410 5415  
 Thr Gly Thr Cys Thr Thr Thr Cys Ala Thr Ala Cys Cys Cys Ala  
 5420 5425 5430  
 Thr Cys Thr Cys Thr Thr Thr Ala Thr Cys Cys Thr Thr Ala Cys  
 5435 5440 5445  
 Cys Thr Ala Thr Thr Gly Thr Thr Thr Gly Thr Cys Gly Cys Ala  
 5450 5455 5460  
 Ala Gly Thr Thr Thr Thr Gly Cys Gly Thr Gly Thr Thr Ala Thr  
 5465 5470 5475  
 Ala Thr Ala Thr Cys Ala Thr Thr Ala Ala Ala Ala Cys Gly Gly  
 5480 5485 5490

## A-743 PCT.ST25.txt

Thr Ala Ala Thr Ala Gly Ala Thr Thr Gly Ala Cys Ala Thr Thr  
 5495 5500 5505  
 Thr Gly Ala Thr Thr Cys Thr Ala Ala Thr Ala Ala Ala Thr Thr  
 5510 5515 5520  
 Gly Gly Ala Thr Thr Thr Thr Thr Gly Thr Cys Ala Cys Ala Cys  
 5525 5530 5535  
 Thr Ala Thr Thr Ala Thr Ala Thr Cys Gly Cys Thr Thr Gly Ala  
 5540 5545 5550  
 Ala Ala Thr Ala Cys Ala Ala Thr Thr Gly Thr Thr Thr Ala Ala  
 5555 5560 5565  
 Cys Ala Thr Ala Ala Gly Thr Ala Cys Cys Thr Gly Thr Ala Gly  
 5570 5575 5580  
 Gly Ala Thr Cys Gly Thr Ala Cys Ala Gly Gly Thr Thr Thr Ala  
 5585 5590 5595  
 Cys Gly Cys Ala Ala Gly Ala Ala Ala Ala Thr Gly Gly Thr Thr  
 5600 5605 5610  
 Thr Gly Thr Thr Ala Thr Ala Gly Thr Cys Gly Ala Thr Thr Ala  
 5615 5620 5625  
 Ala Thr Cys Gly Ala Thr Thr Thr Gly Ala Thr Thr Cys Thr Ala  
 5630 5635 5640  
 Gly Ala Thr Thr Thr Gly Thr Thr Thr Thr Ala Ala Cys Thr Ala  
 5645 5650 5655  
 Ala Thr Thr Ala Ala Ala Gly Gly Ala Gly Gly Ala Ala Thr Ala  
 5660 5665 5670  
 Ala Cys Ala Thr Ala Thr Gly Ala Thr Cys Gly Cys Thr Cys Cys  
 5675 5680 5685  
 Ala Cys Cys Ala Thr Gly Cys Ala Cys Cys Ala Gly Thr Gly Ala  
 5690 5695 5700  
 Gly Ala Ala Gly Cys Ala Thr Thr Ala Thr Gly Ala Gly Cys Ala  
 5705 5710 5715  
 Thr Cys Thr Gly Gly Gly Ala Cys Gly Gly Thr Gly Cys Thr Gly  
 5720 5725 5730  
 Thr Ala Ala Cys Ala Ala Ala Thr Gly Thr Gly Ala Ala Cys Cys  
 5735 5740 5745

## A-743 PCT.ST25.txt

Ala Gly Gly Ala Ala Ala Gly Thr Ala Cys Ala Thr Gly Thr Cys  
 5750 5755 5760  
 Thr Thr Cys Thr Ala Ala Ala Thr Gly Cys Ala Cys Thr Ala Cys  
 5765 5770 5775  
 Thr Ala Cys Cys Thr Cys Thr Gly Ala Cys Ala Gly Thr Gly Thr  
 5780 5785 5790  
 Ala Thr Gly Thr Cys Thr Gly Cys Cys Cys Thr Gly Thr Gly Gly  
 5795 5800 5805  
 Cys Cys Cys Gly Gly Ala Thr Gly Ala Ala Thr Ala Cys Thr Thr  
 5810 5815 5820  
 Gly Gly Ala Thr Ala Gly Cys Thr Gly Gly Ala Ala Thr Gly Ala  
 5825 5830 5835  
 Ala Gly Ala Ala Gly Ala Thr Ala Ala Ala Thr Gly Cys Thr Thr  
 5840 5845 5850  
 Gly Cys Thr Gly Cys Ala Thr Ala Ala Ala Gly Thr Thr Thr Gly  
 5855 5860 5865  
 Thr Gly Ala Thr Ala Cys Ala Gly Gly Cys Ala Ala Gly Gly Cys  
 5870 5875 5880  
 Cys Cys Thr Gly Gly Thr Gly Gly Cys Cys Gly Thr Gly Gly Thr  
 5885 5890 5895  
 Cys Gly Cys Cys Gly Gly Cys Ala Ala Cys Ala Gly Thr Ala Cys  
 5900 5905 5910  
 Gly Ala Cys Cys Cys Cys Cys Cys Gly Gly Cys Gly Cys Thr Gly  
 5915 5920 5925  
 Cys Gly Cys Gly Thr Gly Cys Ala Cys Gly Gly Cys Thr Gly Gly  
 5930 5935 5940  
 Gly Thr Ala Cys Cys Ala Cys Thr Gly Gly Ala Gly Cys Cys Ala  
 5945 5950 5955  
 Gly Gly Ala Cys Thr Gly Cys Gly Ala Gly Thr Gly Cys Thr Gly  
 5960 5965 5970  
 Cys Cys Gly Cys Cys Gly Cys Ala Ala Cys Ala Cys Cys Gly Ala  
 5975 5980 5985  
 Gly Thr Gly Cys Gly Cys Gly Cys Cys Gly Gly Gly Cys Cys Thr  
 5990 5995 6000

A-743 PCT.ST25.txt

Gly Gly Gly Cys Gly Cys Cys Cys Ala Gly Cys Ala Cys Cys Cys  
 6005 6010 6015  
 Gly Thr Thr Gly Cys Ala Gly Cys Thr Cys Ala Ala Cys Ala Ala  
 6020 6025 6030  
 Gly Gly Ala Cys Ala Cys Ala Gly Thr Gly Thr Gly Cys Ala Ala  
 6035 6040 6045  
 Ala Cys Cys Thr Thr Gly Cys Cys Thr Thr Gly Cys Ala Gly Gly  
 6050 6055 6060  
 Cys Thr Ala Cys Thr Thr Cys Thr Cys Thr Gly Ala Thr Gly Cys  
 6065 6070 6075  
 Cys Thr Thr Thr Thr Cys Cys Thr Cys Cys Ala Cys Gly Gly Ala  
 6080 6085 6090  
 Cys Ala Ala Ala Thr Gly Cys Ala Gly Ala Cys Cys Cys Thr Gly  
 6095 6100 6105  
 Gly Ala Cys Cys Ala Ala Cys Thr Gly Thr Ala Cys Cys Thr Thr  
 6110 6115 6120  
 Cys Cys Thr Thr Gly Gly Ala Ala Ala Gly Ala Gly Ala Gly Thr  
 6125 6130 6135  
 Ala Gly Ala Ala Cys Ala Thr Cys Ala Thr Gly Gly Gly Ala Cys  
 6140 6145 6150  
 Ala Gly Ala Gly Ala Ala Ala Thr Cys Cys Gly Ala Thr Gly Thr  
 6155 6160 6165  
 Gly Gly Thr Thr Thr Gly Cys Ala Gly Thr Thr Cys Thr Thr Cys  
 6170 6175 6180  
 Thr Cys Thr Gly Cys Cys Ala Gly Cys Thr Ala Gly Ala Ala Ala  
 6185 6190 6195  
 Ala Cys Cys Ala Cys Cys Ala Ala Ala Thr Gly Ala Ala Cys Cys  
 6200 6205 6210  
 Cys Cys Ala Thr Gly Thr Thr Thr Ala Cys Gly Thr Cys Gly Ala  
 6215 6220 6225  
 Cys Ala Ala Ala Ala Cys Thr Cys Ala Cys Ala Cys Ala Thr Gly  
 6230 6235 6240  
 Thr Cys Cys Ala Cys Cys Thr Thr Gly Thr Cys Cys Ala Gly Cys  
 6245 6250 6255

A-743 PCT.ST25.txt

Thr Cys Cys Gly Gly Ala Ala Cys Thr Cys Cys Thr Gly Gly Gly  
 6260 6265 6270  
 Gly Gly Gly Ala Cys Cys Gly Thr Cys Ala Gly Thr Cys Thr Thr  
 6275 6280 6285  
 Cys Cys Thr Cys Thr Thr Cys Cys Cys Cys Cys Ala Ala Ala  
 6290 6295 6300  
 Ala Cys Cys Cys Ala Ala Gly Gly Ala Cys Ala Cys Cys Cys Thr  
 6305 6310 6315  
 Cys Ala Thr Gly Ala Thr Cys Thr Cys Cys Cys Gly Gly Ala Cys  
 6320 6325 6330  
 Cys Cys Cys Thr Gly Ala Gly Gly Thr Cys Ala Cys Ala Thr Gly  
 6335 6340 6345  
 Cys Gly Thr Gly Gly Thr Gly Gly Thr Gly Gly Ala Cys Gly Thr  
 6350 6355 6360  
 Gly Ala Gly Cys Cys Ala Cys Gly Ala Ala Gly Ala Cys Cys Cys  
 6365 6370 6375  
 Thr Gly Ala Gly Gly Thr Cys Ala Ala Gly Thr Thr Cys Ala Ala  
 6380 6385 6390  
 Cys Thr Gly Gly Thr Ala Cys Gly Thr Gly Gly Ala Cys Gly Gly  
 6395 6400 6405  
 Cys Gly Thr Gly Gly Ala Gly Gly Thr Gly Cys Ala Thr Ala Ala  
 6410 6415 6420  
 Thr Gly Cys Cys Ala Ala Gly Ala Cys Ala Ala Ala Gly Cys Cys  
 6425 6430 6435  
 Gly Cys Gly Gly Gly Ala Gly Gly Ala Gly Cys Ala Gly Thr Ala  
 6440 6445 6450  
 Cys Ala Ala Cys Ala Gly Cys Ala Cys Gly Thr Ala Cys Cys Gly  
 6455 6460 6465  
 Thr Gly Thr Gly Gly Thr Cys Ala Gly Cys Gly Thr Cys Cys Thr  
 6470 6475 6480  
 Cys Ala Cys Cys Gly Thr Cys Cys Thr Gly Cys Ala Cys Cys Ala  
 6485 6490 6495  
 Gly Gly Ala Cys Thr Gly Gly Cys Thr Gly Ala Ala Thr Gly Gly  
 6500 6505 6510

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Cys Ala Ala Gly Gly Ala Gly Thr Ala Cys Ala Ala Gly Thr Gly  
 6515 6520 6525

Cys Ala Ala Gly Gly Thr Cys Thr Cys Cys Ala Ala Cys Ala Ala  
 6530 6535 6540

Ala Gly Cys Cys Cys Thr Cys Cys Cys Ala Gly Cys Cys Cys Cys  
 6545 6550 6555

Cys Ala Thr Cys Gly Ala Gly Ala Ala Ala Ala Cys Cys Ala Thr  
 6560 6565 6570

Cys Thr Cys Cys Ala Ala Ala Gly Cys Cys Ala Ala Ala Gly Gly  
 6575 6580 6585

Gly Cys Ala Gly Cys Cys Cys Cys Gly Ala Gly Ala Ala Cys Cys  
 6590 6595 6600

Ala Cys Ala Gly Gly Thr Gly Thr Ala Cys Ala Cys Cys Cys Thr  
 6605 6610 6615

Gly Cys Cys Cys Cys Cys Ala Thr Cys Cys Cys Gly Gly Gly Ala  
 6620 6625 6630

Thr Gly Ala Gly Cys Thr Gly Ala Cys Cys Ala Ala Gly Ala Ala  
 6635 6640 6645

Cys Cys Ala Gly Gly Thr Cys Ala Gly Cys Cys Thr Gly Ala Cys  
 6650 6655 6660

Cys Thr Gly Cys Cys Thr Gly Gly Thr Cys Ala Ala Ala Gly Gly  
 6665 6670 6675

Cys Thr Thr Cys Thr Ala Thr Cys Cys Cys Ala Gly Cys Gly Ala  
 6680 6685 6690

Cys Ala Thr Cys Gly Cys Cys Gly Thr Gly Gly Ala Gly Thr Gly  
 6695 6700 6705

Gly Gly Ala Gly Ala Gly Cys Ala Ala Thr Gly Gly Gly Cys Ala  
 6710 6715 6720

Gly Cys Cys Gly Gly Ala Gly Ala Ala Cys Ala Ala Cys Thr Ala  
 6725 6730 6735

Cys Ala Ala Gly Ala Cys Cys Ala Cys Gly Cys Cys Thr Cys Cys  
 6740 6745 6750

Cys Gly Thr Gly Cys Thr Gly Gly Ala Cys Thr Cys Cys Gly Ala  
 6755 6760 6765



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Cys Gly Gly Cys Thr Cys Cys Thr Thr Cys Thr Thr Cys Cys Thr  
 6770 6775 6780  
 Cys Thr Ala Cys Ala Gly Cys Ala Ala Gly Cys Thr Cys Ala Cys  
 6785 6790 6795  
 Cys Gly Thr Gly Gly Ala Cys Ala Ala Gly Ala Gly Cys Ala Gly  
 6800 6805 6810  
 Gly Thr Gly Gly Cys Ala Gly Cys Ala Gly Gly Gly Gly Ala Ala  
 6815 6820 6825  
 Cys Gly Thr Cys Thr Thr Cys Thr Cys Ala Thr Gly Cys Thr Cys  
 6830 6835 6840  
 Cys Gly Thr Gly Ala Thr Gly Cys Ala Thr Gly Ala Gly Gly Cys  
 6845 6850 6855  
 Thr Cys Thr Gly Cys Ala Cys Ala Ala Cys Cys Ala Cys Thr Ala  
 6860 6865 6870  
 Cys Ala Cys Gly Cys Ala Gly Ala Ala Gly Ala Gly Cys Cys Thr  
 6875 6880 6885  
 Cys Thr Cys Cys Cys Thr Gly Thr Cys Thr Cys Cys Gly Gly Gly  
 6890 6895 6900  
 Thr Ala Ala Ala Thr Ala Ala Thr Gly Gly Ala Thr Cys Cys Gly  
 6905 6910 6915  
 Cys Gly Gly Ala Ala Ala Gly Ala Ala Gly Ala Ala Gly Ala Ala  
 6920 6925 6930  
 Gly Ala Ala Gly Ala Ala Gly Ala Ala Ala Gly Cys Cys Cys Gly  
 6935 6940 6945  
 Ala Ala Ala Gly Gly Ala Ala Gly Cys Thr Gly Ala Gly Thr Thr  
 6950 6955 6960  
 Gly Gly Cys Thr Gly Cys Thr Gly Cys Cys Ala Cys Cys Gly Cys  
 6965 6970 6975  
 Thr Gly Ala Gly Cys Ala Ala Thr Ala Ala Cys Thr Ala Gly Cys  
 6980 6985 6990  
 Ala Thr Ala Ala Cys Cys Cys Cys Thr Thr Gly Gly Gly Gly Cys  
 6995 7000 7005  
 Cys Thr Cys Thr Ala Ala Ala Cys Gly Gly Gly Thr Cys Thr Thr  
 7010 7015 7020

## A-743 PCT.ST25.txt

Gly Ala Gly Gly Gly Gly Thr Thr Thr Thr Thr Thr Gly Cys Thr  
 7025 7030 7035  
 Gly Ala Ala Ala Gly Gly Ala Gly Gly Ala Ala Cys Cys Gly Cys  
 7040 7045 7050  
 Thr Cys Thr Thr Cys Ala Cys Gly Cys Thr Cys Thr Thr Cys Ala  
 7055 7060 7065  
 Cys Gly Cys Gly Gly Ala Thr Ala Ala Ala Thr Ala Ala Gly Thr  
 7070 7075 7080  
 Ala Ala Cys Gly Ala Thr Cys Cys Gly Gly Thr Cys Cys Ala Gly  
 7085 7090 7095  
 Thr Ala Ala Thr Gly Ala Cys Cys Thr Cys Ala Gly Ala Ala Cys  
 7100 7105 7110  
 Thr Cys Cys Ala Thr Cys Thr Gly Gly Ala Thr Thr Thr Gly Thr  
 7115 7120 7125  
 Thr Cys Ala Gly Ala Ala Cys Gly Cys Thr Cys Gly Gly Thr Thr  
 7130 7135 7140  
 Gly Cys Cys Gly Cys Cys Gly Gly Gly Cys Gly Thr Thr Thr Thr  
 7145 7150 7155  
 Thr Thr Ala Thr Thr Gly Gly Thr Gly Ala Gly Ala Ala Thr Cys  
 7160 7165 7170  
 Gly Cys Ala Gly Cys Ala Ala Cys Thr Thr Gly Thr Cys Gly Cys  
 7175 7180 7185  
 Gly Cys Cys Ala Ala Thr Cys Gly Ala Gly Cys Cys Ala Thr Gly  
 7190 7195 7200  
 Thr Cys Gly Thr Cys Gly Thr Cys Ala Ala Cys Gly Ala Cys Cys  
 7205 7210 7215  
 Cys Cys Cys Cys Ala Thr Thr Cys Ala Ala Gly Ala Ala Cys Ala  
 7220 7225 7230  
 Gly Cys Ala Ala Gly Cys Ala Gly Cys Ala Thr Thr Gly Ala Gly  
 7235 7240 7245  
 Ala Ala Cys Thr Thr Thr Gly Gly Ala Ala Thr Cys Cys Ala Gly  
 7250 7255 7260  
 Thr Cys Cys Cys Thr Cys Thr Thr Cys Cys Ala Cys Cys Thr Gly  
 7265 7270 7275

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Cys Thr Gly Ala Cys Cys Gly  
7280 7285

<210> 29  
<211> 14  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Preferred TALL-1 Modulating Domains  
<400> 29

Pro Gly Thr Cys Phe Pro Phe Pro Trp Glu Cys Thr His Ala  
1 5 10

<210> 30  
<211> 14  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Preferred TALL-1 Modulating Domains  
<400> 30

Trp Gly Ala Cys Trp Pro Phe Pro Trp Glu Cys Phe Lys Glu  
1 5 10

<210> 31  
<211> 14  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Preferred TALL-1 Modulating Domains  
<400> 31

Val Pro Phe Cys Asp Leu Leu Thr Lys His Cys Phe Glu Ala  
1 5 10

<210> 32  
<211> 18  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Preferred TALL-1 Modulating Domains  
<400> 32

Gly Ser Arg Cys Lys Tyr Lys Trp Asp Val Leu Thr Lys Gln Cys Phe  
1 5 10 15

His His

<210> 33  
<211> 18  
<212> PRT

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&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Preferred TALL-1 Modulating Domains

&lt;400&gt; 33

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Pro | Gly | Cys | Lys | Trp | Asp | Leu | Leu | Ile | Lys | Gln | Trp | Val | Cys | Asp |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

Pro Leu

&lt;210&gt; 34

&lt;211&gt; 18

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Preferred TALL-1 Modulating Domains

&lt;400&gt; 34

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Ala | Asp | Cys | Tyr | Phe | Asp | Ile | Leu | Thr | Lys | Ser | Asp | Val | Cys | Thr |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

Ser Ser

&lt;210&gt; 35

&lt;211&gt; 18

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Preferred TALL-1 Modulating Domains

&lt;400&gt; 35

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Asp | Asp | Cys | Met | Tyr | Asp | Gln | Leu | Thr | Arg | Met | Phe | Ile | Cys | Ser |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

Asn Leu

&lt;210&gt; 36

&lt;211&gt; 18

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Preferred TALL-1 Modulating Domains

&lt;400&gt; 36

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asp | Leu | Asn | Cys | Lys | Tyr | Asp | Glu | Leu | Thr | Tyr | Lys | Glu | Trp | Cys | Gln |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

Phe Asn

A-743 PCT.ST25.txt

<210> 37  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 Modulating Domains

<400> 37

Phe His Asp Cys Lys Tyr Asp Leu Leu Thr Arg Gln Met Val Cys His  
 1 5 10 15

Gly Leu

<210> 38  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 Modulating Domains

<400> 38

Arg Asn His Cys Phe Trp Asp His Leu Leu Lys Gln Asp Ile Cys Pro  
 1 5 10 15

Ser Pro

<210> 39  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 Modulating Domains

<400> 39

Ala Asn Gln Cys Trp Trp Asp Ser Leu Thr Lys Lys Asn Val Cys Glu  
 1 5 10 15

Phe Phe

<210> 40  
 <211> 8  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Polyglycine linkers

<400> 40  
 gggkggg

8

<210> 41

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<211> 8  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Polyglycine linkers

<220>  
 <221> misc\_feature  
 <222> (4)..(4)  
 <223> N is asparagine

<400> 41  
 gggngsgg

8

<210> 42  
 <211> 8  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Polyglycine linkers

<400> 42  
 gggcgggg

8

<210> 43  
 <211> 5  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Polyglycine linkers

<400> 43

Gly Pro Asn Gly Gly  
 1 5

<210> 44  
 <211> 19  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Peptide Bond

<220>  
 <221> misc\_feature  
 <222> (19)..(19)  
 <223> Xaa = a peptide bond  
 Fc domain attached at Position 19 to C-terminus

<400> 44

Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp Val Cys Asp  
 1 5 10 15

Pro Leu Xaa

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<210> 45  
 <211> 19  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Peptide bond

<220>  
 <221> misc\_feature  
 <222> (1)..(1)  
 <223> Xaa = a peptide bond  
 Fc domain attached at Position 1 to N-terminus

<400> 45

Xaa Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp Val Cys  
 1                      5                      10                      15

Asp Pro Leu

<210> 46  
 <211> 38  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Peptide bond

<220>  
 <221> misc\_feature  
 <222> (38)..(38)  
 <223> Xaa = a peptide bond  
 Fc domain attached at Position 38 to C-terminus

<220>  
 <221> misc\_feature  
 <222> (19)..(19)  
 <223> Xaa = a peptide bond

<400> 46

Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp Val Cys Asp  
 1                      5                      10                      15

Pro Leu Xaa Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp  
                     20                      25                      30

Val Cys Asp Pro Leu Xaa  
                     35

<210> 47  
 <211> 38  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Peptide bond

A-743 PCT.ST25.txt

<220>  
 <221> misc\_feature  
 <222> (1)..(1)  
 <223> Xaa = a peptide bond  
 Fc domain attached at Position 1 to N-terminus

<220>  
 <221> misc\_feature  
 <222> (20)..(20)  
 <223> Xaa = a peptide bond

<400> 47

Xaa Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp Val Cys  
 1 5 10 15

Asp Pro Leu Xaa Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln  
 20 25 30

Trp Val Cys Asp Pro Leu  
 35

<210> 48  
 <211> 19  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Peptide bond

<220>  
 <221> misc\_feature  
 <222> (19)..(19)  
 <223> Xaa = a peptide bond  
 Fc domain attached at Position 19 to C-terminus

<400> 48

Ser Ala Asp Cys Tyr Phe Asp Ile Leu Thr Lys Ser Asp Val Cys Thr  
 1 5 10 15

Ser Ser Xaa

<210> 49  
 <211> 19  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Peptide bond

<220>  
 <221> misc\_feature  
 <222> (1)..(1)  
 <223> Xaa = a peptide bond  
 Fc domain attached at Position 1 to N-terminus

<400> 49



## A-743 PCT.ST25.txt

Xaa Ser Ala Asp Cys Tyr Phe Asp Ile Leu Thr Lys Ser Asp Val Cys  
 1 5 10 15

Thr Ser Ser

<210> 50  
 <211> 36  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Peptide bond

<220>  
 <221> misc\_feature  
 <222> (36)..(36)  
 <223> Xaa = a peptide bond  
 Fc domain attached at Position 36 to C-terminus

<220>  
 <221> misc\_feature  
 <222> (18)..(18)  
 <223> Xaa = a peptide bond

<400> 50

Ser Ala Asp Cys Tyr Phe Asp Ile Leu Thr Lys Ser Asp Val Thr Ser  
 1 5 10 15

Ser Xaa Ser Ala Asp Cys Tyr Phe Asp Ile Leu Thr Lys Ser Asp Val  
 20 25 30

Thr Ser Ser Xaa  
 35

<210> 51  
 <211> 36  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Peptide bond

<220>  
 <221> misc\_feature  
 <222> (1)..(1)  
 <223> Xaa = a peptide bond  
 Fc domain attached at Position 1 to N-terminus

<220>  
 <221> misc\_feature  
 <222> (19)..(19)  
 <223> Xaa = a peptide bond

<400> 51

Xaa Ser Ala Asp Cys Tyr Phe Asp Ile Leu Thr Lys Ser Asp Val Thr  
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1 5 10 15

Ser Ser Xaa Ser Ala Asp Cys Tyr Phe Asp Ile Leu Thr Lys Ser Asp  
20 25 30

Val Thr Ser Ser  
35

<210> 52  
<211> 19  
<212> PRT  
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<220>  
<223> Peptide bond

<220>  
<221> misc\_feature  
<222> (19)..(19)  
<223> Xaa = a peptide bond  
Fc domain attached at Position 19 to C-terminus

<400> 52

Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Cys His  
1 5 10 15

Gly Leu Xaa

<210> 53  
<211> 19  
<212> PRT  
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<220>  
<223> Peptide bond

<220>  
<221> misc\_feature  
<222> (1)..(1)  
<223> Xaa = a peptide bond  
Fc domain attached at Position 1 to N-terminus

<400> 53

Xaa Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Cys  
1 5 10 15

His Gly Leu

<210> 54  
<211> 38  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Peptide bond

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<220>  
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 <222> (19)..(19)  
 <223> Xaa = a peptide bond

<220>  
 <221> misc\_feature  
 <222> (38)..(38)  
 <223> Xaa = a peptide bond  
 Fc domain attached at Position 38 to C-terminus

<400> 54

Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Cys His  
 1 5 10 15

Gly Leu Xaa Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Trp  
 20 25 30

Val Cys His Gly Leu Xaa  
 35

<210> 55  
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 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Peptide bond

<220>  
 <221> misc\_feature  
 <222> (1)..(1)  
 <223> Xaa = a peptide bond  
 Fc domain attached at Position 1 to N-terminus

<220>  
 <221> misc\_feature  
 <222> (20)..(20)  
 <223> Xaa = a peptide bond

<400> 55

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 1 5 10 15

His Gly Leu Xaa Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln  
 20 25 30

Trp Val Cys His Gly Leu  
 35

<210> 56  
 <211> 25  
 <212> DNA  
 <213> Artificial Sequence

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&lt;220&gt;

&lt;223&gt; Oligonucleotide

&lt;400&gt; 56

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25

&lt;210&gt; 57

&lt;211&gt; 26

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Oligonucleotide

&lt;400&gt; 57

catgtaccgt aacactgagt ttcgtc

26

&lt;210&gt; 58

&lt;211&gt; 18

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Consensus peptide

&lt;400&gt; 58

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | His | Asp | Cys | Lys | Trp | Asp | Leu | Leu | Thr | Lys | Gln | Trp | Val | Cys | His |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

Gly Leu

&lt;210&gt; 59

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Preferred linker sequence

&lt;400&gt; 59

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Ser | Gly | Ser | Ala | Thr | Gly | Gly | Ser | Gly | Ser | Thr | Ala | Ser | Ser | Gly |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|
| Ser | Gly | Ser | Ala | Thr | His | Met |
|     |     |     |     | 20  |     |     |

&lt;210&gt; 60

&lt;211&gt; 18

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Preferred TALL-1 modulating domains

&lt;400&gt; 60

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asn | Gln | Thr | Leu | Trp | Lys | Trp | Asp | Leu | Leu | Thr | Lys | Gln | Phe | Ile | Thr |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

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Tyr Met

<210> 61  
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<220>  
<223> Preferred TALL-1 modulating domains

&lt;400&gt; 61

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Val | Tyr | Gln | Gly | Trp | Trp | Asp | Thr | Leu | Thr | Lys | Leu | Tyr | Ile | Trp |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

Asp Gly

<210> 62  
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<220>  
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&lt;400&gt; 62

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Trp | Leu | Asp | Gly | Gly | Trp | Arg | Asp | Pro | Leu | Ile | Lys | Arg | Ser | Val | Gln |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

Leu Gly

<210> 63  
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<220>  
<223> Preferred TALL-1 modulating domains

&lt;400&gt; 63

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | His | Gln | Gln | Phe | Lys | Trp | Asp | Leu | Leu | Thr | Lys | Gln | Trp | Val | Gln |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

Ser Asn

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<220>  
<223> Preferred TALL-1 modulating domains

&lt;400&gt; 64

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Gln Arg Val Gly Gln Phe Trp Asp Val Leu Thr Lys Met Phe Ile Thr  
 1 5 10 15

Gly Ser

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Trp Pro

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<220>  
 <223> Preferred TALL-1 modulating domains

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 1 5 10 15

Trp Met

<210> 67  
 <211> 18  
 <212> PRT  
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<220>  
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Gly His Pro Thr Tyr Lys Trp Asp Leu Leu Thr Lys Gln Trp Ile Leu  
 1 5 10 15

Gln Met

<210> 68  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

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&lt;220&gt;

&lt;223&gt; Preferred TALL-1 modulating domains

&lt;400&gt; 68

Trp Asn Asn Trp Ser Leu Trp Asp Pro Leu Thr Lys Leu Trp Leu Gln  
 1 5 10 15

Gln Asn

&lt;210&gt; 69

&lt;211&gt; 18

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Preferred TALL-1 modulating domains

&lt;400&gt; 69

Trp Gln Trp Gly Trp Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Gln  
 1 5 10 15

Gln Gln

&lt;210&gt; 70

&lt;211&gt; 18

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Preferred TALL-1 modulating domains

&lt;400&gt; 70

Gly Gln Met Gly Trp Arg Trp Asp Pro Leu Thr Lys Met Trp Leu Gly  
 1 5 10 15

Thr Ser

&lt;210&gt; 71

&lt;211&gt; 62

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Oligonucleotides

&lt;400&gt; 71

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gg 62

&lt;210&gt; 72

&lt;211&gt; 64

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

A-743 PCT.ST25.txt

&lt;220&gt;

&lt;223&gt; Oligonucleotides

&lt;400&gt; 72

tcgacccac cgcctcctgg agcgtgagtg cattcccacg ggaagccgaa acaagtaccc 60

ggca

64

&lt;210&gt; 73

&lt;211&gt; 62

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Oligonucleotides

&lt;400&gt; 73

tatgtggggt gcttgttggc cgttcccggtg ggaatgtttc aaagaaggtg gaggcggtgg 60

gg

62

&lt;210&gt; 74

&lt;211&gt; 64

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Oligonucleotides

&lt;400&gt; 74

tcgacccac cgcctccacc ttctttgaaa cattcccacg ggaacggcca acaagcaccc 60

caca

64

&lt;210&gt; 75

&lt;211&gt; 62

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Oligonucleotides

&lt;400&gt; 75

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gg

62

&lt;210&gt; 76

&lt;211&gt; 64

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Oligonucleotides

&lt;400&gt; 76

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acca

64

&lt;210&gt; 77

&lt;211&gt; 74

&lt;212&gt; DNA



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&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Oligonucleotides

&lt;400&gt; 77

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tggaggcggt gggg 74

&lt;210&gt; 78

&lt;211&gt; 76

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Oligonucleotides

&lt;400&gt; 78

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ttacaacgag aaccca 76

&lt;210&gt; 79

&lt;211&gt; 74

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Oligonucleotides

&lt;400&gt; 79

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tggaggcggt gggg 74

&lt;210&gt; 80

&lt;211&gt; 76

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Oligonucleotides

&lt;400&gt; 80

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ttacaaccg gcagca 76

&lt;210&gt; 81

&lt;211&gt; 74

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Oligonucleotides

&lt;400&gt; 81

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tggaggcggt gggg 74

&lt;210&gt; 82

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 tggaggcggt gggg 74  
  
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 ttacagttca ggtcca 76

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<210> 98

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tggagcatct ggtcgcattg ggtcaccagc aaatcgcgct gttagcgggc ccattaagtt    660
ctgtctcggc gcgtctgcgt ctggctggct ggcatataa tctcactcgc aatcaaattc    720
agccgatagc ggaacgggaa ggcgactgga gtgccatgtc cggttttcaa caaacatgc    780
aatgctgaa tgagggcatc gttcccactg cgatgctggt tgccaacgat cagatggcgc    840
tggggcgaat gcgcgccatt accgagtccg ggctgcgcgt tggcgcggat atctcggtag    900
tgggatacga cgataccgaa gacagctcat gttatatccc gccgttaacc accatcaaac    960
aggattttcg cctgctgggg caaacagcgc tggaccgctt gctgcaactc tctcagggcc   1020
aggcggtgaa gggcaatcag ctgttgcccg tctcactggt gaaaagaaaa accaccctgg   1080
cgcccaatac gcaaaccgcc tctccccgcg cgttggccga ttcattaatg cagctggcac   1140
gacaggtttc ccgactggaa agcggacagt aaggtacatc aggatccagg cacagga     1197

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<210> 100  
 <211> 14  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Modulators of TALL-1

<220>  
 <221> misc\_feature  
 <222> (1, 2, 3, 13)..(14)  
 <223> Xaa (Pos1,2,3,13,14) are each independently absent or amino acid residues;

<220>  
 <221> misc\_feature  
 <222> (6)..(6)  
 <223> Xaa (Pos6) is an amino acid residue; Xaa (Pos9) is a basic or hydrophobic residue;

<220>  
 <221> misc\_feature  
 <222> (12)..(12)  
 <223> Xaa (Pos12) is a neutral hydrophobic residue.

<400> 100

```

Xaa Xaa Xaa Cys Asp Xaa Leu Thr Xaa Xaa Cys Xaa Xaa Xaa
1           5           10

```

<210> 101  
 <211> 14  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Modulators of TALL-1

<220>  
 <221> misc\_feature  
 <222> (1, 2, 3, 12 and)..(13)  
 <223> Xaa (Pos1,2,3,12,13) are each independently absent or amino acid

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residues;

<220>  
 <221> misc\_feature  
 <222> (5 and)..(8)  
 <223> Xaa (Pos5,8) is a neutral hydrophobic residue; Xaa (Pos10) is an acidic residue;

<220>  
 <221> misc\_feature  
 <222> (14)..(14)  
 <223> Xaa (Pos14) is absent or is an amino acid residue.

&lt;400&gt; 101

Xaa Xaa Xaa Cys Xaa Pro Phe Xaa Trp Xaa Cys Xaa Xaa Xaa  
 1 5 10

<210> 102  
 <211> 14  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Modulator of TALL-1

<220>  
 <221> misc\_feature  
 <222> (1, 2, 3, 12, 13 and)..(14)  
 <223> Xaa (Pos1,2,3,12,13,14) are each independently absent or amino acid residues;

<220>  
 <221> misc\_feature  
 <222> (6 and)..(7)  
 <223> Xaa (Pos6,7) is a hydrophobic residue;

<220>  
 <221> misc\_feature  
 <222> (10)..(10)  
 <223> Xaa (Pos10) is an acidic or polar hydrophobic residue.

&lt;400&gt; 102

Xaa Xaa Xaa Xaa Trp Xaa Xaa Trp Gly Xaa Xaa Xaa Xaa Xaa  
 1 5 10

<210> 103  
 <211> 14  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Modulator of TALL-1

<220>  
 <221> misc\_feature  
 <222> (1)..(1)  
 <223> Xaa (Pos1) is absent or is an amino acid residue;



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<220>  
 <221> misc\_feature  
 <222> (2 and)..(14)  
 <223> Xaa (Pos2,14) is a neutral hydrophobic residue;

<220>  
 <221> misc\_feature  
 <222> (3 and)..(10)  
 <223> Xaa (Pos3,10) is an amino acid residue;

<220>  
 <221> misc\_feature  
 <222> (5, 6, 7, 8, 12 and)..(13)  
 <223> Xaa (Pos5,6,7,8,12,13) are each independently amino acid residues  
 ;

<220>  
 <221> misc\_feature  
 <222> (9)..(9)  
 <223> Xaa (Pos9) is an acidic residue.

<400> 103

Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa  
 1 5 10

<210> 104  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Modulator of TALL-1

<220>  
 <221> misc\_feature  
 <222> (1, 2, 12, 13, 16, 17 and)..(18)  
 <223> Xaa (Pos1,2,12,13,16,17,18) are each independently absent or amino acid residues;

<220>  
 <221> misc\_feature  
 <222> (3)..(3)  
 <223> Xaa (Pos3) is an acidic or amide residue;

<220>  
 <221> misc\_feature  
 <222> (5 and)..(8)  
 <223> Xaa (Pos5,8) is an amino acid residue;

<220>  
 <221> misc\_feature  
 <222> (6)..(6)  
 <223> Xaa (Pos6) is an aromatic residue;

<220>  
 <221> misc\_feature  
 <222> (11)..(11)

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&lt;223&gt; Xaa (Pos11) is a basic residue;

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (14)..(14)

&lt;223&gt; Xaa (Pos14) is a neutral hydrophobic residue.

&lt;400&gt; 104

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Xaa | Xaa | Xaa | Cys | Xaa | Xaa | Asp | Xaa | Leu | Thr | Xaa | Xaa | Xaa | Xaa | Cys | Xaa |
| 1   |     |     | 5   |     |     |     |     | 10  |     |     |     |     |     | 15  |     |

Xaa Xaa

&lt;210&gt; 105

&lt;211&gt; 18

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Modulator of TALL-1

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1, 2 and)..(3)

&lt;223&gt; Xaa (Pos1,2,3) are each independently absent or amino acid residues;

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (5, 7, 14 and)..(16)

&lt;223&gt; Xaa (Pos5,7,14,16) is an amino acid residue;

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (10)..(10)

&lt;223&gt; Xaa (Pos10) is a basic residue;

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (11 and)..(12)

&lt;223&gt; Xaa (Pos11,12) are each independently amino acid residues;

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (13 and)..(17)

&lt;223&gt; Xaa (Pos13,17) is a neutral hydrophobic residue;

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (18)..(18)

&lt;223&gt; Xaa (Pos18) is an amino acid residue or is absent.

&lt;400&gt; 105

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Xaa | Xaa | Xaa | Cys | Xaa | Asp | Xaa | Leu | Thr | Xaa | Xaa | Xaa | Xaa | Xaa | Cys | Xaa |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|

1 5 A-743 PCT.ST25.txt 10 15

Xaa Xaa

```

<210> 106
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Modulator of TALL-1

<220>
<221> misc_feature
<222> (1, 2, 3, 16, 17 and)..(18)
<223> Xaa (Pos1,2,3,16,17,18) are each independently absent or amino acid
      id residues;

<220>
<221> misc_feature
<222> (5, 6, 7, 10, 13 and)..(14)
<223> Xaa (Pos5,6,7,10,13,14) are each independently amino acid residue
      s.

```

<400> 106

Xaa Xaa Xaa Cys Xaa Xaa Xaa Trp Asp Xaa Leu Thr Xaa Xaa Cys Xaa  
1 5 10 15

Xaa Xaa

```

<210> 107
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Modulator of TALL-1

<220>
<221> misc_feature
<222> (1,2,3,15,16,17)..(18)
<223> Xaa (Pos1,2,3,15,16,17,18) are each independently absent or amino
      acid residues;

<220>
<221> misc_feature
<222> (5, 6, 7, 9 and)..(13)
<223> Xaa (Pos 5,6,7,9 13) are each independently amino acid residues;

<220>
<221> misc_feature
<222> (11)..(11)
<223> Xaa (Pos 11) is T or I; and

<400> 107

```

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Xaa Xaa Xaa Cys Xaa Xaa Xaa Asp Xaa Leu Xaa Lys Xaa Cys Xaa Xaa  
 1 5 10 15

Xaa Xaa

<210> 108  
 <211> 4  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Modulator of TALL-1  
 <220>  
 <221> misc\_feature  
 <222> (2)..(2)  
 <223> X at (Pos 2) is an amino acid residue

<220>  
 <221> misc\_feature  
 <222> (4)..(4)  
 <223> X at (Pos 4) is threonyl or isoleucyl

&lt;400&gt; 108

Asp Xaa Leu Xaa  
 1

<210> 109  
 <211> 14  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Modulator of TALL-1  
 <220>  
 <221> misc\_feature  
 <222> (1, 2 and)..(3)  
 <223> X at (Pos 1, 2, 3) are absent or are amino acid residues (with on  
 e of X1, X2, and X3 preferred to be C when one of X12,  
 X13, an  
 d X14 is C);

<220>  
 <221> misc\_feature  
 <222> (5)..(5)  
 <223> X at (Pos 5) is W, Y, or F (W preferred);

<220>  
 <221> misc\_feature  
 <222> (7)..(7)  
 <223> X at (Pos 7) is an amino acid residue (L preferred);

<220>  
 <221> misc\_feature  
 <222> (9)..(9)  
 <223> X at (Pos 9) is T or I (T preferred);

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```

<220>
<221> misc_feature
<222> (10)..(10)
<223> X at (Pos 10) is K, R, or H ( K preferred).

<220>
<221> misc_feature
<222> (12)..(12)
<223> X at (Pos 12) is C, a neutral hydrophobic residue, or a basic residue (W, C, or R preferred);

<220>
<221> misc_feature
<222> (13)..(13)
<223> X at (Post 13) is C, a neutral hydrophobic residue or is absent (V preferred);

<220>
<221> misc_feature
<222> (14)..(14)
<223> X at (Pos 14) is any amino acid residue or is absent.

```

&lt;400&gt; 109

```

Xaa Xaa Xaa Lys Xaa Asp Xaa Leu Xaa Xaa Gln Xaa Xaa Xaa
1           5           10

```

```

<210> 110
<211> 5
<212> PRT
<213> Artificial Sequence

```

```

<220>
<223> Modulator of TALL-1

```

&lt;400&gt; 110

```

Pro Phe Pro Trp Glu
1           5

```

```

<210> 111
<211> 248
<212> PRT
<213> Artificial Sequence

```

```

<220>
<223> TALL-1 inhibitory peptibodies

```

&lt;400&gt; 111

```

Met Pro Gly Thr Cys Phe Pro Phe Pro Trp Glu Cys Thr His Ala Gly
1           5           10           15

```

```

Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
20           25           30

```

```

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
35           40           45

```

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Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val  
50 55 60

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val  
65 70 75 80

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln  
85 90 95

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln  
100 105 110

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala  
115 120 125

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro  
130 135 140

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr  
145 150 155 160

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser  
165 170 175

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr  
180 185 190

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr  
195 200 205

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe  
210 215 220

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys  
225 230 235 240

Ser Leu Ser Leu Ser Pro Gly Lys  
245

&lt;210&gt; 112

&lt;211&gt; 248

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; TALL-1 inhibitory peptibodies

&lt;400&gt; 112

Met Trp Gly Ala Cys Trp Pro Phe Pro Trp Glu Cys Phe Lys Glu Gly  
1 5 10 15

Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala  
Page 70

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20

25

30

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro  
           35                          40                          45

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val  
       50                          55                          60

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val  
   65                          70                          75                          80

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln  
                           85                          90                          95

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln  
           100                          105                          110

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala  
       115                          120                          125

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro  
       130                          135                          140

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr  
   145                          150                          155                          160

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser  
                           165                          170                          175

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr  
           180                          185                          190

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr  
       195                          200                          205

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe  
       210                          215                          220

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys  
   225                          230                          235                          240

Ser Leu Ser Leu Ser Pro Gly Lys  
                           245

&lt;210&gt; 113

&lt;211&gt; 248

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; TALL-1 inhibitory peptibodies

&lt;400&gt; 113

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Met Val Pro Phe Cys Asp Leu Leu Thr Lys His Cys Phe Glu Ala Gly  
 1 5 10 15

Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala  
 20 25 30

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro  
 35 40 45

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val  
 50 55 60

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val  
 65 70 75 80

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln  
 85 90 95

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln  
 100 105 110

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala  
 115 120 125

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro  
 130 135 140

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr  
 145 150 155 160

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser  
 165 170 175

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr  
 180 185 190

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr  
 195 200 205

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe  
 210 215 220

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys  
 225 230 235 240

Ser Leu Ser Leu Ser Pro Gly Lys  
 245

<210> 114  
 <211> 252  
 <212> PRT



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&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; TALL-1 inhibitory peptibodies

&lt;400&gt; 114

Met Gly Ser Arg Cys Lys Tyr Lys Trp Asp Val Leu Thr Lys Gln Cys  
 1 5 10 15

Phe His His Gly Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro  
 20 25 30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe  
 35 40 45

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val  
 50 55 60

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe  
 65 70 75 80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro  
 85 90 95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr  
 100 105 110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val  
 115 120 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala  
 130 135 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg  
 145 150 155 160

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly  
 165 170 175

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro  
 180 185 190

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser  
 195 200 205

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln  
 210 215 220

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His  
 225 230 235 240

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys  
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250

245

<210> 115  
<211> 252  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> TALL-1 inhibitory peptibodies

<400> 115

Met Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp Val Cys  
1 5 10 15

Asp Pro Leu Gly Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro  
20 25 30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe  
35 40 45

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val  
50 55 60

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe  
65 70 75 80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro  
85 90 95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr  
100 105 110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val  
115 120 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala  
130 135 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg  
145 150 155 160

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly  
165 170 175

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro  
180 185 190

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser  
195 200 205

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln  
210 215 220

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Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His  
 225 230 235 240

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys  
 245 250

<210> 116

<211> 252

<212> PRT

<213> Artificial Sequence

<220>

<223> TALL-1 inhibitory peptibodies

<400> 116

Met Ser Ala Asp Cys Tyr Phe Asp Ile Leu Thr Lys Ser Asp Val Cys  
 1 5 10 15

Thr Ser Ser Gly Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro  
 20 25 30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe  
 35 40 45

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val  
 50 55 60

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe  
 65 70 75 80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro  
 85 90 95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr  
 100 105 110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val  
 115 120 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala  
 130 135 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg  
 145 150 155 160

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly  
 165 170 175

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro  
 180 185 190

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser  
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|  |     |     |
|--|-----|-----|
| 195  | 200 | 205 |
| Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln<br>210 215 220     |     |     |
| Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His<br>225 230 235 240 |     |     |
| Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys<br>245 250                         |     |     |
| <210> 117  |     |     |
| <211> 252  |     |     |
| <212> PRT  |     |     |
| <213> Artificial Sequence  |     |     |
| <220>  |     |     |
| <223> TALL-1 inhibitory peptibodies  |     |     |
| <400> 117  |     |     |
| Met Ser Asp Asp Cys Met Tyr Asp Gln Leu Thr Arg Met Phe Ile Cys<br>1 5 10 15       |     |     |
| Ser Asn Leu Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro<br>20 25 30            |     |     |
| Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe<br>35 40 45        |     |     |
| Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val<br>50 55 60        |     |     |
| Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe<br>65 70 75 80     |     |     |
| Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro<br>85 90 95        |     |     |
| Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr<br>100 105 110     |     |     |
| Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val<br>115 120 125     |     |     |
| Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala<br>130 135 140     |     |     |
| Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg<br>145 150 155 160 |     |     |
| Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly<br>165 170 175     |     |     |

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Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro  
 180 185 190

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser  
 195 200 205

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln  
 210 215 220

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His  
 225 230 235 240

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys  
 245 250

<210> 118

<211> 252

<212> PRT

<213> Artificial Sequence

<220>

<223> TALL-1 inhibitory peptibodies

<400> 118

Met Asp Leu Asn Cys Lys Tyr Asp Glu Leu Thr Tyr Lys Glu Trp Cys  
 1 5 10 15

Gln Phe Asn Gly Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro  
 20 25 30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe  
 35 40 45

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val  
 50 55 60

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe  
 65 70 75 80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro  
 85 90 95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr  
 100 105 110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val  
 115 120 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala  
 130 135 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg  
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```

145                               150      A-743 PCT.ST25.txt      155                               160

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
      165                               170                               175

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
      180                               185                               190

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
      195                               200                               205

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
      210                               215                               220

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
      225                               230                               235                               240

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
      245                               250

<210> 119
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> TALL-1 inhibitory peptibodies

<400> 119

Met Phe His Asp Cys Lys Tyr Asp Leu Leu Thr Arg Gln Met Val Cys
1      5      10

His Gly Leu Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro
      20      25      30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
      35      40      45

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
      50      55      60

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
65      70      75      80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
      85      90      95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
      100      105      110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
      115      120      125

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Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala  
 130 135 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg  
 145 150 155 160

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly  
 165 170 175

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro  
 180 185 190

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser  
 195 200 205

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln  
 210 215 220

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His  
 225 230 235 240

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys  
 245 250

<210> 120

<211> 252

<212> PRT

<213> Artificial Sequence

<220>

<223> TALL-1 inhibitory peptibodies

<400> 120

Met Arg Asn His Cys Phe Trp Asp His Leu Leu Lys Gln Asp Ile Cys  
 1 5 10 15

Pro Ser Pro Gly Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro  
 20 25 30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe  
 35 40 45

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val  
 50 55 60

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe  
 65 70 75 80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro  
 85 90 95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr  
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100

105

110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val  
 115 120 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala  
 130 135 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg  
 145 150 155 160

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly  
 165 170 175

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro  
 180 185 190

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser  
 195 200 205

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln  
 210 215 220

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His  
 225 230 235 240

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys  
 245 250

&lt;210&gt; 121

&lt;211&gt; 252

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; TALL-1 inhibitory peptibodies

&lt;400&gt; 121

Met Ala Asn Gln Cys Trp Trp Asp Ser Leu Thr Lys Lys Asn Val Cys  
 1 5 10 15

Glu Phe Phe Gly Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro  
 20 25 30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe  
 35 40 45

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val  
 50 55 60

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe  
 65 70 75 80



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Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro  
85 90 95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr  
100 105 110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val  
115 120 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala  
130 135 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg  
145 150 155 160

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly  
165 170 175

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro  
180 185 190

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser  
195 200 205

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln  
210 215 220

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His  
225 230 235 240

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys  
245 250

<210> 122  
<211> 252  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> TALL-1 inhibitory peptibodies

<400> 122

Met Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Cys  
1 5 10 15

His Gly Leu Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro  
20 25 30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe  
35 40 45

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val  
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50

55

60

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe  
65 70 75 80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro  
85 90 95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr  
100 105 110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val  
115 120 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala  
130 135 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg  
145 150 155 160

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly  
165 170 175

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro  
180 185 190

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser  
195 200 205

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln  
210 215 220

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His  
225 230 235 240

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys  
245 250

&lt;210&gt; 123

&lt;211&gt; 293

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; TALL-1 inhibitory peptibodies

&lt;400&gt; 123

Met Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp Val Cys  
1 5 10 15

Asp Pro Leu Gly Ser Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala  
20 25 30

## A-743 PCT.ST25.txt

Ser Ser Gly Ser Gly Ser Ala Thr His Met Leu Pro Gly Cys Lys Trp  
 35 40 45  
 Asp Leu Leu Ile Lys Gln Trp Val Cys Asp Pro Leu Gly Gly Gly Gly  
 50 55 60  
 Gly Val Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu  
 65 70 75 80  
 Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr  
 85 90 95  
 Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val  
 100 105 110  
 Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val  
 115 120 125  
 Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser  
 130 135 140  
 Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu  
 145 150 155 160  
 Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala  
 165 170 175  
 Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro  
 180 185 190  
 Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln  
 195 200 205  
 Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala  
 210 215 220  
 Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr  
 225 230 235 240  
 Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu  
 245 250 255  
 Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser  
 260 265 270  
 Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser  
 275 280 285  
 Leu Ser Pro Gly Lys  
 290

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<210> 124  
 <211> 293  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> TALL-1 inhibitory peptibodies

<400> 124

Met Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Cys  
 1 5 10 15

His Gly Leu Gly Ser Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala  
 20 25 30

Ser Ser Gly Ser Gly Ser Ala Thr His Met Phe His Asp Cys Lys Trp  
 35 40 45

Asp Leu Leu Thr Lys Gln Trp Val Cys His Gly Leu Gly Gly Gly Gly  
 50 55 60

Gly Val Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu  
 65 70 75 80

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr  
 85 90 95

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val  
 100 105 110

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val  
 115 120 125

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser  
 130 135 140

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu  
 145 150 155 160

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala  
 165 170 175

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro  
 180 185 190

Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln  
 195 200 205

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala  
 210 215 220

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr  
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<210> 125
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Consensus Sequence

<220>
<221> misc_feature
<222> (1, 2 and)..(3)
<223> X at (Pos 1, 2, 3) are absent or are amino acid residues (with on
      e of X1, X2, and X3 preferred to be C when one of X12,
      X13, and X14 is C);

<220>
<221> misc_feature
<222> (7)..(7)
<223> X at (Pos 7) is an amino acid residue (L preferred);

<220>
<221> misc_feature
<222> (9)..(9)
<223> X at (Pos 9) is T or I (T preferred);

<220>
<221> misc_feature
<222> (12)..(12)
<223> X at (Pos 12) is C, a neutral hydrophobic residue, or a basic res
      idue (W, C, or R
      preferred);

<220>
<221> misc_feature
<222> (13)..(13)
<223> X at (Pos 13) is C, a neutral hydrophobic residue or is absent (V

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preferred);

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (14)..(14)

&lt;223&gt; X at (Pos 14) is any amino acid residue or is absent.

&lt;400&gt; 125

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Xaa | Xaa | Xaa | Lys | Trp | Asp | Xaa | Leu | Xaa | Lys | Gln | Xaa | Xaa | Xaa |
| 1   |     |     |     | 5   |     |     |     |     |     | 10  |     |     |     |

&lt;210&gt; 126

&lt;211&gt; 18

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Preferred TALL-1 modulating domains

&lt;400&gt; 126

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Tyr | Lys | Gly | Arg | Gln | Met | Trp | Asp | Ile | Leu | Thr | Arg | Ser | Trp | Val | Val |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

Ser Leu

&lt;210&gt; 127

&lt;211&gt; 18

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Preferred TALL-1 modulating domains

&lt;400&gt; 127

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gln | Asp | Val | Gly | Leu | Trp | Trp | Asp | Ile | Leu | Thr | Arg | Ala | Trp | Met | Pro |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

Asn Ile

&lt;210&gt; 128

&lt;211&gt; 18

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Preferred TALL-1 modulating domains

&lt;400&gt; 128

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gln | Asn | Ala | Gln | Arg | Val | Trp | Asp | Leu | Leu | Ile | Arg | Thr | Trp | Val | Tyr |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

Pro Gln

A-743 PCT.ST25.txt

<210> 129  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains

<400> 129

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Trp | Asn | Glu | Ala | Trp | Trp | Asp | Glu | Leu | Thr | Lys | Ile | Trp | Val | Leu |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

Glu Gln

<210> 130  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains

<400> 130

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Ile | Thr | Cys | Asp | Thr | Trp | Asp | Ser | Leu | Ile | Lys | Lys | Cys | Val | Pro |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

Gln Ser

<210> 131  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains

<400> 131

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Ala | Ile | Met | Gln | Phe | Trp | Asp | Ser | Leu | Thr | Lys | Thr | Trp | Leu | Arg |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

Gln Ser

<210> 132  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains

<400> 132

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Trp | Leu | His | Ser | Gly | Trp | Trp | Asp | Pro | Leu | Thr | Lys | His | Trp | Leu | Gln |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

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Lys Val

<210> 133  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains  
 <400> 133

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Glu | Trp | Phe | Phe | Trp | Phe | Asp | Pro | Leu | Thr | Arg | Ala | Gln | Leu | Lys |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

Phe Arg

<210> 134  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains  
 <400> 134

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Val | Trp | Phe | Trp | Trp | Phe | Asp | Pro | Leu | Thr | Lys | Gln | Trp | Thr | Gln |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

Ala Gly

<210> 135  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains  
 <400> 135

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Gln | Cys | Lys | Gly | Tyr | Tyr | Asp | Ile | Leu | Thr | Lys | Trp | Cys | Val | Thr |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

Asn Gly

<210> 136  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains  
 <400> 136



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Leu Trp Ser Lys Glu Val Trp Asp Ile Leu Thr Lys Ser Trp Val Ser  
 1 5 10 15

Gln Ala

<210> 137  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains

<400> 137

Lys Ala Ala Gly Trp Trp Phe Asp Trp Leu Thr Lys Val Trp Val Pro  
 1 5 10 15

Ala Pro

<210> 138  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains

<400> 138

Ala Tyr Gln Thr Trp Phe Trp Asp Ser Leu Thr Arg Leu Trp Leu Ser  
 1 5 10 15

Thr Thr

<210> 139  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains

<400> 139

Ser Gly Gln His Phe Trp Trp Asp Leu Leu Thr Arg Ser Trp Thr Pro  
 1 5 10 15

Ser Thr

<210> 140  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

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&lt;220&gt;

&lt;223&gt; Preferred TALL-1 modulating domains

&lt;400&gt; 140

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Gly | Val | Gly | Gln | Lys | Trp | Asp | Pro | Leu | Thr | Lys | Gln | Trp | Val | Ser |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

Arg Gly

&lt;210&gt; 141

&lt;211&gt; 18

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Preferred TALL-1 modulating domains

&lt;400&gt; 141

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Gly | Lys | Met | Cys | Gln | Trp | Asp | Pro | Leu | Ile | Lys | Arg | Thr | Val | Cys |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

Val Gly

&lt;210&gt; 142

&lt;211&gt; 18

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Preferred TALL-1 modulating domains

&lt;400&gt; 142

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Cys | Arg | Gln | Gly | Ala | Lys | Phe | Asp | Leu | Leu | Thr | Lys | Gln | Cys | Leu | Leu |
| 1   |     |     |     | 5   |     |     |     | 10  |     |     |     |     |     | 15  |     |

Gly Arg

&lt;210&gt; 143

&lt;211&gt; 18

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Preferred TALL-1 modulating domains

&lt;400&gt; 143

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Gln | Ala | Ile | Arg | His | Trp | Asp | Val | Leu | Thr | Lys | Gln | Trp | Val | Asp |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

Ser Gln

&lt;210&gt; 144

A-743 PCT.ST25.txt

<211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains

<400> 144

Arg Gly Pro Cys Gly Ser Trp Asp Leu Leu Thr Lys His Cys Leu Asp  
 1 5 10 15

Ser Gln

<210> 145  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains

<400> 145

Trp Gln Trp Lys Gln Gln Trp Asp Leu Leu Thr Lys Gln Met Val Trp  
 1 5 10 15

Val Gly

<210> 146  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains

<400> 146

Pro Ile Thr Ile Cys Arg Lys Asp Leu Leu Thr Lys Gln Val Val Cys  
 1 5 10 15

Leu Asp

<210> 147  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains

<400> 147

Lys Thr Cys Asn Gly Lys Trp Asp Leu Leu Thr Lys Gln Cys Leu Gln  
 1 5 10 15

Gln Ala

A-743 PCT.ST25.txt

<210> 148  
<211> 18  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Preferred TALL-1 modulating domains

<400> 148

Lys Cys Leu Lys Gly Lys Trp Asp Leu Leu Thr Lys Gln Cys Val Thr  
1 5 10 15

Glu Val

<210> 149  
<211> 18  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Preferred TALL-1 modulating domains

<400> 149

Arg Cys Trp Asn Gly Lys Trp Asp Leu Leu Thr Lys Gln Cys Ile His  
1 5 10 15

Pro Trp

<210> 150  
<211> 18  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Preferred TALL-1 modulating domains

<400> 150

Asn Arg Asp Met Arg Lys Trp Asp Pro Leu Ile Lys Gln Trp Ile Val  
1 5 10 15

Arg Pro

<210> 151  
<211> 18  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Preferred TALL-1 modulating domains

<400> 151

Gln Ala Ala Ala Ala Thr Trp Asp Leu Leu Thr Lys Gln Trp Leu Val  
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1                      5                      10                      15

Pro Pro

<210> 152  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains

&lt;400&gt; 152

Pro Glu Gly Gly Pro Lys Trp Asp Pro Leu Thr Lys Gln Phe Leu Pro  
 1                      5                      10                      15

Pro Val

<210> 153  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains

&lt;400&gt; 153

Gln Thr Pro Gln Lys Lys Trp Asp Leu Leu Thr Lys Gln Trp Phe Thr  
 1                      5                      10                      15

Arg Asn

<210> 154  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains

&lt;400&gt; 154

Ile Gly Ser Pro Cys Lys Trp Asp Leu Leu Thr Lys Gln Met Ile Cys  
 1                      5                      10                      15

Gln Thr

<210> 155  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains

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&lt;400&gt; 155

Cys Thr Ala Ala Gly Lys Trp Asp Leu Leu Thr Lys Gln Cys Ile Gln  
 1 5 10 15

Glu Lys

&lt;210&gt; 156

&lt;211&gt; 18

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Preferred TALL-1 modulating domains

&lt;400&gt; 156

Val Ser Gln Cys Met Lys Trp Asp Leu Leu Thr Lys Gln Cys Leu Gln  
 1 5 10 15

Gly Trp

&lt;210&gt; 157

&lt;211&gt; 18

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Preferred TALL-1 modulating domains

&lt;400&gt; 157

Val Trp Gly Thr Trp Lys Trp Asp Leu Leu Thr Lys Gln Tyr Leu Pro  
 1 5 10 15

Pro Gln

&lt;210&gt; 158

&lt;211&gt; 18

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Preferred TALL-1 modulating domains

&lt;400&gt; 158

Gly Trp Trp Glu Met Lys Trp Asp Leu Leu Thr Lys Gln Trp Tyr Arg  
 1 5 10 15

Pro Gln

&lt;210&gt; 159

&lt;211&gt; 18

&lt;212&gt; PRT

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&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Preferred TALL-1 modulating domains

&lt;400&gt; 159

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Ala | Gln | Val | Ser | Lys | Trp | Asp | Leu | Leu | Thr | Lys | Gln | Trp | Leu | Pro |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

Leu Ala

&lt;210&gt; 160

&lt;211&gt; 18

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Preferred TALL-1 modulating domains

&lt;400&gt; 160

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gln | Leu | Trp | Gly | Thr | Lys | Trp | Asp | Leu | Leu | Thr | Lys | Gln | Tyr | Ile | Gln |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

Ile Met

&lt;210&gt; 161

&lt;211&gt; 18

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Preferred TALL-1 modulating domains

&lt;400&gt; 161

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Trp | Ala | Thr | Ser | Gln | Lys | Trp | Asp | Leu | Leu | Thr | Lys | Gln | Trp | Val | Gln |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

Asn Met

&lt;210&gt; 162

&lt;211&gt; 18

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Preferred TALL-1 modulating domains

&lt;400&gt; 162

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gln | Arg | Gln | Cys | Ala | Lys | Trp | Asp | Leu | Leu | Thr | Lys | Gln | Cys | Val | Leu |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

Phe Tyr

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<210> 163  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains

<400> 163

Lys Thr Thr Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Arg Ile Cys  
 1 5 10 15

Gln Val

<210> 164  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains

<400> 164

Leu Leu Cys Gln Gly Lys Trp Asp Leu Leu Thr Lys Gln Cys Leu Lys  
 1 5 10 15

Leu Arg

<210> 165  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains

<400> 165

Leu Met Trp Phe Trp Lys Trp Asp Leu Leu Thr Lys Gln Leu Val Pro  
 1 5 10 15

Thr Phe

<210> 166  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains

<400> 166

Gln Thr Trp Ala Trp Lys Trp Asp Leu Leu Thr Lys Gln Trp Ile Gly  
 1 5 10 15



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Pro Met

<210> 167  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains  
 <400> 167

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asn | Lys | Glu | Leu | Leu | Lys | Trp | Asp | Leu | Leu | Thr | Lys | Gln | Cys | Arg | Gly |
| 1   |     |     | 5   |     |     |     |     |     | 10  |     |     |     |     | 15  |     |

Arg Ser

<210> 168  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains  
 <400> 168

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Gln | Lys | Asp | Leu | Lys | Trp | Asp | Leu | Leu | Thr | Lys | Gln | Tyr | Val | Arg |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

Gln Ser

<210> 169  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains  
 <400> 169

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Lys | Pro | Cys | Gln | Lys | Trp | Asp | Leu | Leu | Thr | Lys | Gln | Cys | Leu | Gly |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

Ser Val

<210> 170  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains  
 <400> 170

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Gly Gln Ile Gly Trp Lys Trp Asp Leu Leu Thr Lys Gln Trp Ile Gln  
 1 5 10 15

Thr Arg

<210> 171  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains

<400> 171

Val Trp Leu Asp Trp Lys Trp Asp Leu Leu Thr Lys Gln Trp Ile His  
 1 5 10 15

Pro Gln

<210> 172  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains

<400> 172

Gln Glu Trp Glu Tyr Lys Trp Asp Leu Leu Thr Lys Gln Trp Gly Trp  
 1 5 10 15

Leu Arg

<210> 173  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains

<400> 173

His Trp Asp Ser Trp Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Val  
 1 5 10 15

Gln Ala

<210> 174  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

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&lt;220&gt;

&lt;223&gt; Preferred TALL-1 modulating domains

&lt;400&gt; 174

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Arg | Pro | Leu | Gln | Lys | Trp | Asp | Leu | Leu | Thr | Lys | Gln | Trp | Leu | Arg |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

Val Gly

&lt;210&gt; 175

&lt;211&gt; 18

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Preferred TALL-1 modulating domains

&lt;400&gt; 175

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Asp | Gln | Trp | Gln | Lys | Trp | Asp | Leu | Leu | Thr | Lys | Gln | Trp | Phe | Trp |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

Asp Val

&lt;210&gt; 176

&lt;211&gt; 18

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Preferred TALL-1 modulating domains

&lt;400&gt; 176

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gln | Gln | Thr | Phe | Met | Lys | Trp | Asp | Leu | Leu | Thr | Lys | Gln | Trp | Ile | Arg |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

Arg His

&lt;210&gt; 177

&lt;211&gt; 18

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Preferred TALL-1 modulating domains

&lt;400&gt; 177

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gln | Gly | Glu | Cys | Arg | Lys | Trp | Asp | Leu | Leu | Thr | Lys | Gln | Cys | Phe | Pro |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

Gly Gln

&lt;210&gt; 178

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<211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains

<400> 178

Gly Gln Met Gly Trp Arg Trp Asp Pro Leu Ile Lys Met Cys Leu Gly  
 1 5 10 15

Pro Ser

<210> 179  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains

<400> 179

Gln Leu Asp Gly Cys Lys Trp Asp Leu Leu Thr Lys Gln Lys Val Cys  
 1 5 10 15

Ile Pro

<210> 180  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains

<400> 180

His Gly Tyr Trp Gln Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Ser  
 1 5 10 15

Ser Glu

<210> 181  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains

<400> 181

His Gln Gly Gln Cys Gly Trp Asp Leu Leu Thr Arg Ile Tyr Leu Pro  
 1 5 10 15

Cys His

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<210> 182  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains  
 <400> 182

Leu His Lys Ala Cys Lys Trp Asp Leu Leu Thr Lys Gln Cys Trp Pro  
 1 5 10 15

Met Gln

<210> 183  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains  
 <400> 183

Gly Pro Pro Gly Ser Val Trp Asp Leu Leu Thr Lys Ile Trp Ile Gln  
 1 5 10 15

Thr Gly

<210> 184  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains  
 <400> 184

Ile Thr Gln Asp Trp Arg Phe Asp Thr Leu Thr Arg Leu Trp Leu Pro  
 1 5 10 15

Leu Arg

<210> 185  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains  
 <400> 185

Gln Gly Gly Phe Ala Ala Trp Asp Val Leu Thr Lys Met Trp Ile Thr  
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1                      5                      10                      15

Val Pro

<210> 186  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains

&lt;400&gt; 186

Gly His Gly Thr Pro Trp Trp Asp Ala Leu Thr Arg Ile Trp Ile Leu  
 1                      5                      10                      15

Gly Val

<210> 187  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains

&lt;400&gt; 187

Val Trp Pro Trp Gln Lys Trp Asp Leu Leu Thr Lys Gln Phe Val Phe  
 1                      5                      10                      15

Gln Asp

<210> 188  
 <211> 19  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Preferred TALL-1 modulating domains

&lt;400&gt; 188

Trp Gln Gln Trp Ser Trp Lys Trp Asp Leu Leu Thr Arg Gln Tyr Ile  
 1                      5                      10                      15

Ser Ser Ser

<210> 189  
 <211> 882  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> TALL-1 12-3 tandem dimer

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<400> 189
atgcttccag gctgcaagtg ggatcttctt attaagcaat gggatatgca tccacttgga      60
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catatgctgc cgggttgtaa atgggacctg ctgatcaaac agtgggtttg tgacccgctg      180
gggtggaggcg gtggggtcga caaaactcac acatgtccac cttgtccagc tccggaactc      240
ctgggggggac cgtcagtctt cctcttcccc caaaaaccca aggacaccct catgatctcc      300
cggacccttg aggtcacatg cgtgggtggtg gacgtgagcc acgaagaccc tgaggtcaag      360
ttcaactggt acgtggacgg cgtggagggtg cataatgcca agacaaagcc gcgggaggag      420
cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg      480
aatggcaagg agtacaagtg caaggtctcc aacaaagccc tcccagcccc catcgagaaa      540
accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gccccatcc      600
cgggatgagc tgaccaagaa ccaggtcagc ctgacctgcc tgggtcaaagg cttctatccc      660
agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg      720
cctcccgtgc tggactccga cggctccttc ttctctaca gcaagctcac cgtggacaag      780
agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcattgaggc tctgcacaac      840
cactacacgc agaagagcct ctccctgtct ccgggtaaat aa                        882

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<210> 190
<211> 23
<212> PRT
<213> Artificial Sequence

```

```

<220>
<223> Preferred linker

```

```

<400> 190

```

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Gly Ser Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser Ser Gly
1           5           10          15

```

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Ser Gly Ser Ala Thr Gly Met
                20

```

```

<210> 191
<211> 23
<212> PRT
<213> Artificial Sequence

```

```

<220>
<223> Preferred linker

```

```

<400> 191

```

```

Gly Ser Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser Ser Gly
1           5           10          15

```

```

Ser Gly Ser Ala Thr Gly Ser
                20

```

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Ser Gly Ser Ala Thr Xaa Xaa Gly Ser Gly Ser Ala Thr Gly Gly Ser  
                   20                  25                  30

Gly Ser Thr Ala Ser Ser Gly Ser Gly Ser Ala Thr Xaa Xaa  
           35                  40                  45

<210> 195  
 <211> 38  
 <212> PRT  
 <213> Human

<400> 195

Met Arg Arg Gly Pro Arg Ser Leu Arg Gly Arg Asp Ala Pro Val Pro  
 1                  5                  10                  15

Thr Pro Cys Val Pro Thr Glu Cys Tyr Asp Leu Leu Val Arg Lys Cys  
           20                  25                  30

Val Asp Cys Arg Leu Leu  
           35

<210> 196  
 <211> 41  
 <212> PRT  
 <213> Human

<400> 196

Thr Ile Cys Asn His Gln Ser Gln Arg Thr Cys Ala Ala Phe Cys Arg  
 1                  5                  10                  15

Ser Leu Ser Cys Arg Lys Glu Gln Gly Lys Phe Tyr Asp His Leu Leu  
           20                  25                  30

Arg Asp Cys Ile Ser Cys Ala Ser Ile  
           35                  40

<210> 197  
 <211> 42  
 <212> PRT  
 <213> Human

<400> 197

Phe Val Ser Pro Ser Gln Glu Ile Arg Gly Arg Phe Arg Arg Met Leu  
 1                  5                  10                  15

Gln Met Ala Gly Gln Cys Ser Gln Asn Glu Tyr Phe Asp Ser Leu Leu  
           20                  25                  30

His Ala Cys Ile Pro Cys Gln Leu Arg Cys  
           35                  40



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International Bureau



(43) International Publication Date  
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[Continued on next page]

(54) Title: PEPTIDES AND RELATED MOLECULES THAT BIND TO TALL-1

$a^1a^2a^3CDa^4La^5a^6a^{10}Ca^{12}a^{13}a^{14}$

(SEQ. ID. NO: 100),

$b^1b^2b^3Cb^5b^6Db^8Lb^{10}b^{11}b^{12}b^{13}b^{14}Cb^{16}b^{17}b^{18}$

(SEQ. ID. NO: 104)

$c^1c^2c^3Cc^5Dc^7Lc^9c^{10}c^{11}c^{12}c^{13}c^{14}Cc^{16}c^{17}c^{18}$

(SEQ. ID. NO: 105)

$d^1d^2d^3Cd^5d^6d^7WDd^{10}Ld^{13}d^{14}d^{15}Cd^{16}d^{17}d^{18}$

(SEQ. ID. NO: 106)

$e^1e^2e^3Ce^5e^6e^7De^9Le^{11}Ke^{13}Ce^{15}e^{16}e^{17}e^{18}$

(SEQ. ID. NO: 107)

$f^1f^2f^3Kf^5Df^7Lf^9f^{10}Qf^{12}f^{13}f^{14}$

(SEQ. ID NO: 109)

$(X^1)_n-V^1-(X^2)_m$  (I)

(57) Abstract: The present invention concerns therapeutic agents that modulate the activity of TALL-1. In accordance with the present invention, modulators of TALL-1 may comprise an amino acid sequence  $Dz^2Lz^4$  wherein  $z^2$  is an amino acid residue and  $z^4$  is threonyl or isoleucyl. Exemplary molecules comprise a sequence of the formulae  $a^1a^2a^3CDa^4La^5a^6a^{10}Ca^{12}a^{13}a^{14}$  (SEQ.ID.NO:100),  $b^1b^2b^3Cb^5b^6Db^8Lb^{10}b^{11}b^{12}b^{13}b^{14}Cb^{16}b^{17}b^{18}$  (SEQ.ID.NO:104),  $c^1c^2c^3Cc^5Dc^7Lc^9c^{10}c^{11}c^{12}c^{13}c^{14}Cc^{16}c^{17}c^{18}$  (SEQ.ID.NO:105),  $d^1d^2d^3Cd^5d^6d^7WDd^{10}Ld^{13}d^{14}d^{15}Cd^{16}d^{17}d^{18}$  (SEQ.ID.NO:106),  $e^1e^2e^3Ce^5e^6e^7De^9Le^{11}Ke^{13}Ce^{15}e^{16}e^{17}e^{18}$  (SEQ.ID.NO:107),  $f^1f^2f^3Kf^5Df^7Lf^9f^{10}Qf^{12}f^{13}f^{14}$  (SEQ.ID NO:109) wherein the substituents are as defined in the specification. The invention further comprises compositions of matter of the formula  $(X^1)_n-V^1-(X^2)_m$ , wherein  $V^1$  is a vehicle that is covalently attached to one or more of the above TALL-1 modulating compositions of matter. The vehicle and the TALL-1 modulating composition of matter may be linked through the N- or C-terminus of the TALL-1 modulating portion. The preferred vehicle is an Fc domain, and the preferred Fc domain is an IgG Fc domain.



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21 August 2003

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/15273

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : C07K 14/52, 14/525; A61K 38/19; C12N 5/10, 15/28

US CL : 530/351, 402; 514/2, 8, 12; 536/23.5; 435/69.1, 71.1, 471, 320.1, 325, 252.3, 254.11

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/351, 402; 514/2, 8, 12; 536/23.5; 435/69.1, 71.1, 471, 320.1, 325, 252.3, 254.11

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
NONEElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
Please See Continuation Sheet**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category * | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No. |
|------------|--|-----------------------|
| A          | Database PNAS, SHU, H.-B. et al. B cell maturation protein is a receptor for the tumor necrosis factor family member TALL-1. Proc. Natl. Acad. Sci. USA. 01 August 2000, Vol. 97, No. 16, pages 9156-9161. | 1-62                  |
| A          | Database PNAS, KHARE et al. Severe B cell hyperplasia and autoimmune disease in TALL-1 transgenic mice. Proc. Natl. Acad. Sci. USA. 28 March 2000, Vol. 97, No. 7, pages 3370-3375.                        | 1-62                  |

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

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INTERNATIONAL SEARCH REPORT

PCT/US02/15273

**Continuation of B. FIELDS SEARCHED Item 3:**

CAS ONLINE, MEDLINE, CAPLUS, EMBASE, USPATFULL

search terms: TALL-1, binding composition, ligand, hybrid, chimera, DNA, expression vector, host cell, administering, treatment, therapy

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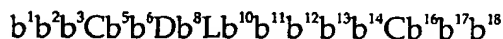
- (51) International Patent Classification<sup>7</sup>: C07K (74) Agents: ODRE, Steven et al.; Amgen, Inc., One Amgen Center Drive, M/S 27-4-A, Thousand Oaks, CA 91320-1799 (US).
- (21) International Application Number: PCT/US02/15273
- (22) International Filing Date: 13 May 2002 (13.05.2002) (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.
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- (72) Inventors: MIN, Hosung; 3875 Conner Court, Newbury Park, CA 91320 (US). HSU, Hailing; 11623 Blossomwood, Moorpark, CA 93021 (US).
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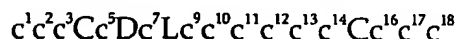
(54) Title: PEPTIDES AND RELATED MOLECULES THAT BIND TO TALL-1



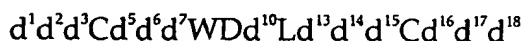
(SEQ. ID. NO: 100),



(SEQ. ID. NO: 104)



(SEQ. ID. NO: 105)



(SEQ. ID. NO: 106)

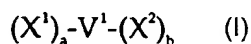


(SEQ. ID. NO: 107)



(SEQ. ID NO: 109)

(57) Abstract: The present invention concerns therapeutic agents that modulate the activity of TALL-1. In accordance with the present invention, modulators of TALL-1 may comprise an amino acid sequence Dz<sup>2</sup>Lz<sup>4</sup> wherein z<sup>2</sup> is an amino acid residue and z<sup>4</sup> is threonyl or isoleucyl. Exemplary molecules comprise a sequence of the formulae a<sup>1</sup>a<sup>2</sup>a<sup>3</sup>CDa<sup>6</sup>La<sup>8</sup>a<sup>9</sup>a<sup>10</sup>Ca<sup>12</sup>a<sup>13</sup>a<sup>14</sup> (SEQ.ID.NO:100), b<sup>1</sup>b<sup>2</sup>b<sup>3</sup>Cb<sup>5</sup>b<sup>6</sup>Db<sup>8</sup>Lb<sup>10</sup>b<sup>11</sup>b<sup>12</sup>b<sup>13</sup>b<sup>14</sup>Cb<sup>16</sup>b<sup>17</sup>b<sup>18</sup> (SEQ.ID.NO:104), c<sup>1</sup>c<sup>2</sup>c<sup>3</sup>Cc<sup>5</sup>Dc<sup>7</sup>Lc<sup>9</sup>c<sup>10</sup>c<sup>11</sup>c<sup>12</sup>c<sup>13</sup>c<sup>14</sup>Cc<sup>16</sup>c<sup>17</sup>c<sup>18</sup> (SEQ.ID.NO:105), d<sup>1</sup>d<sup>2</sup>d<sup>3</sup>Cd<sup>5</sup>d<sup>6</sup>d<sup>7</sup>WDd<sup>10</sup>Ld<sup>13</sup>d<sup>14</sup>d<sup>15</sup>Cd<sup>16</sup>d<sup>17</sup>d<sup>18</sup> (SEQ.ID.NO:106), e<sup>1</sup>e<sup>2</sup>e<sup>3</sup>Ce<sup>5</sup>e<sup>6</sup>e<sup>7</sup>De<sup>9</sup>Le<sup>11</sup>Ke<sup>13</sup>Ce<sup>15</sup>e<sup>16</sup>e<sup>17</sup>e<sup>18</sup> (SEQ.ID.NO:107) f<sup>1</sup>f<sup>2</sup>f<sup>3</sup>Kf<sup>5</sup>Df<sup>7</sup>Lf<sup>9</sup>f<sup>10</sup>Qf<sup>12</sup>f<sup>13</sup>f<sup>14</sup> (SEQ.ID NO:109) wherein the substituents are as defined in the specification. The invention further comprises compositions of matter of the formula (X<sup>1</sup>)<sub>a</sub>-V<sup>1</sup>-(X<sup>2</sup>)<sub>b</sub> wherein V<sup>1</sup> is a vehicle that is covalently attached to one or more of the above TALL-1 modulating compositions of matter. The vehicle and the TALL-1 modulating composition of matter may be linked through the N- or C-terminus of the TALL-1 modulating portion. The preferred vehicle is an Fc domain, and the preferred Fc domain is an IgG Fc domain.





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## PEPTIDES AND RELATED MOLECULES THAT BIND TO TALL-1

This application is related to U.S. provisional application no. 60/290,196,  
5 filed May 11, 2001, which is hereby incorporated by reference.

### Background of the Invention

After years of study in necrosis of tumors, tumor necrosis factors (TNFs)  $\alpha$  and  $\beta$  were finally cloned in 1984. The ensuing years witnessed  
10 the emergence of a superfamily of TNF cytokines, including fas ligand (FasL), CD27 ligand (CD27L), CD30 ligand (CD30L), CD40 ligand (CD40L), TNF-related apoptosis-inducing ligand (TRAIL, also designated AGP-1), osteoprotegerin binding protein (OPG-BP or OPG ligand), 4-1BB ligand, LIGHT, APRIL, and TALL-1. Smith *et al.* (1994), *Cell* 76: 959-962;  
15 Lacey *et al.* (1998), *Cell* 93: 165-176; Chichepotiche *et al.* (1997), *J. Biol. Chem.* 272: 32401-32410; Mauri *et al.* (1998), *Immunity* 8: 21-30; Hahne *et al.* (1998), *J. Exp. Med.* 188: 1185-90; Shu *et al.* (1999), *J. Leukocyte Biology* 65: 680-3. This family is unified by its structure, particularly at the C-terminus. In addition, most members known to date are expressed in  
20 immune compartments, although some members are also expressed in other tissues or organs, as well. Smith *et al.* (1994), *Cell* 76: 959-62. All ligand members, with the exception of LT- $\alpha$ , are type II transmembrane proteins, characterized by a conserved 150 amino acid region within C-terminal extracellular domain. Though restricted to only 20-25% identity,  
25 the conserved 150 amino acid domain folds into a characteristic  $\beta$ -pleated sheet sandwich and trimerizes. This conserved region can be proteolytically released, thus generating a soluble functional form. Banner *et al.* (1993), *Cell* 73: 431-445.

Many members within this ligand family are expressed in lymphoid enriched tissues and play important roles in the immune system development and modulation. Smith *et al.* (1994). For example, TNF $\alpha$  is mainly synthesized by macrophages and is an important mediator for inflammatory responses and immune defenses. Tracey & Cerami (1994), *Ann. Rev. Med.* 45: 491-503. Fas-L, predominantly expressed in activated T cell, modulates TCR-mediated apoptosis of thymocytes. Nagata, S. & Suda, T. (1995) *Immunology Today* 16: 39-43; Castrim *et al.* (1996), *Immunity* 5: 617-27. CD40L, also expressed by activated T cells, provides an essential signal for B cell survival, proliferation and immunoglobulin isotype switching. Noelle (1996), *Immunity* 4: 415-9.

The cognate receptors for most of the TNF ligand family members have been identified. These receptors share characteristic multiple cysteine-rich repeats within their extracellular domains, and do not possess catalytic motifs within cytoplasmic regions. Smith *et al.* (1994). The receptors signal through direct interactions with death domain proteins (e.g. TRADD, FADD, and RIP) or with the TRAF proteins (e.g. TRAF2, TRAF3, TRAF5, and TRAF6), triggering divergent and overlapping signaling pathways, e.g. apoptosis, NF- $\kappa$ B activation, or JNK activation. Wallach *et al.* (1999), *Annual Review of Immunology* 17: 331-67. These signaling events lead to cell death, proliferation, activation or differentiation. The expression profile of each receptor member varies. For example, TNFR1 is expressed on a broad spectrum of tissues and cells, whereas the cell surface receptor of OPGL is mainly restricted to the osteoclasts. Hsu *et al.* (1999) *Proc. Natl. Acad. Sci. USA* 96: 3540-5.

A number of research groups have recently identified TNF family ligands with the same or substantially similar sequence. The ligand has been variously named neutrokin  $\alpha$  (WO 98/18921, published May 7, 1998), 63954 (WO 98/27114, published June 25, 1998), TL5 (EP 869 180, published October 7, 1998), NTN-2 (WO 98/55620 and WO 98/55621,



published December 10, 1998), TNRL1-alpha (WO 9911791, published March 11, 1999), kay ligand (WO99/12964, published March 18, 1999), and AGP-3 (U.S. Prov. App. Nos. 60/119,906, filed February 12, 1999 and 60/166,271, filed November 18, 1999, respectively); and TALL-1 (WO  
5 00/68378, published Nov. 16, 2000). Each of these references is hereby incorporated by reference. Hereinafter, the ligands reported therein are collectively referred to as TALL-1.

TALL-1 is a member of the TNF ligand superfamily that is functionally involved in B cell survival and proliferation. Transgenic mice  
10 overexpressing TALL-1 had severe B cell hyperplasia and lupus-like autoimmune disease. Khare *et al.* (2000) *PNAS* 97(7):3370-3375). Both TACI and BCMA serve as cell surface receptors for TALL-1. Gross *et al.* (2000), *Nature* 404: 995-999; Ware (2000), *J. Exp. Med.* 192(11): F35-F37; Ware (2000), *Nature* 404: 949-950; Xia *et al.* (2000), *J. Exp. Med.* 192(1):137-  
15 143; Yu *et al.* (2000), *Nature Immunology* 1(3):252-256; Marsters *et al.* (2000), *Current Biology* 10:785-788; Hatzoglou *et al.* (2000) *J. of Immunology* 165:1322-1330; Shu *et al.* (2000) *PNAS* 97(16):9156-9161; Thompson *et al.* (2000) *J. Exp. Med.* 192(1):129-135; Mukhopadhyay *et al.* (1999) *J. Biol. Chem.* 274(23): 15978-81; Shu *et al.* (1999) *J. Leukocyte Biol.*  
20 65:680-683; Gruss *et al.* (1995) *Blood* 85(12): 3378-3404; Smith *et al.* (1994), *Cell* 76: 959-962; U.S. Pat. No. 5,969,102, issued October 19, 1999; WO 00/67034, published November 9, 2000; WO 00/40716, published July 13, 2000; WO 99/35170, published July 15, 1999. Both receptors are expressed on B cells and signal through interaction with TRAF proteins. In addition,  
25 both TACI and BCMA also bind to another TNF ligand family member, APRIL. Yu *et al.* (2000), *Nature Immunology* 1(3) :252-256. APRIL has also been demonstrated to induce B cell proliferation.

To date, no recombinant or modified proteins employing peptide modulators of TALL-1 have been disclosed. Recombinant and modified

proteins are an emerging class of therapeutic agents. Useful modifications of protein therapeutic agents include combination with the "Fc" domain of an antibody and linkage to polymers such as polyethylene glycol (PEG) and dextran. Such modifications are discussed in detail in a patent  
5 application entitled, "Modified Peptides as Therapeutic Agents," published WO 00/24782, which is hereby incorporated by reference in its entirety.

A much different approach to development of therapeutic agents is peptide library screening. The interaction of a protein ligand with its  
10 receptor often takes place at a relatively large interface. However, as demonstrated for human growth hormone and its receptor, only a few key residues at the interface contribute to most of the binding energy. Clackson *et al.* (1995), *Science* 267: 383-6. The bulk of the protein ligand merely displays the binding epitopes in the right topology or serves  
15 functions unrelated to binding. Thus, molecules of only "peptide" length (2 to 40 amino acids) can bind to the receptor protein of a given large protein ligand. Such peptides may mimic the bioactivity of the large protein ligand ("peptide agonists") or, through competitive binding, inhibit the bioactivity of the large protein ligand ("peptide antagonists").

20 Phage display peptide libraries have emerged as a powerful method in identifying such peptide agonists and antagonists. See, for example, Scott *et al.* (1990), *Science* 249: 386; Devlin *et al.* (1990), *Science* 249: 404; U.S. Pat. No. 5,223,409, issued June 29, 1993; U.S. Pat. No. 5,733,731, issued March 31, 1998; U.S. Pat. No. 5,498,530, issued March 12,  
25 1996; U.S. Pat. No. 5,432,018, issued July 11, 1995; U.S. Pat. No. 5,338,665, issued August 16, 1994; U.S. Pat. No. 5,922,545, issued July 13, 1999; WO 96/40987, published December 19, 1996; and WO 98/15833, published April 16, 1998 (each of which is incorporated by reference in its entirety). In such libraries, random peptide sequences are displayed by fusion with

coat proteins of filamentous phage. Typically, the displayed peptides are affinity-eluted against an immobilized target protein. The retained phages may be enriched by successive rounds of affinity purification and repropagation. The best binding peptides may be sequenced to identify  
5 key residues within one or more structurally related families of peptides. See, e.g., Cwirla *et al.* (1997), *Science* 276: 1696-9, in which two distinct families were identified. The peptide sequences may also suggest which residues may be safely replaced by alanine scanning or by mutagenesis at the DNA level. Mutagenesis libraries may be created and screened to  
10 further optimize the sequence of the best binders. Lowman (1997), *Ann. Rev. Biophys. Biomol. Struct.* 26: 401-24.

Structural analysis of protein-protein interaction may also be used to suggest peptides that mimic the binding activity of large protein ligands. In such an analysis, the crystal structure may suggest the identity  
15 and relative orientation of critical residues of the large protein ligand, from which a peptide may be designed. See, e.g., Takasaki *et al.* (1997), *Nature Biotech.* 15: 1266-70. These analytical methods may also be used to investigate the interaction between a receptor protein and peptides selected by phage display, which may suggest further modification of the  
20 peptides to increase binding affinity.

Other methods compete with phage display in peptide research. A peptide library can be fused to the carboxyl terminus of the *lac* repressor and expressed in *E. coli*. Another *E. coli*-based method allows display on the cell's outer membrane by fusion with a peptidoglycan-associated  
25 lipoprotein (PAL). Hereinafter, these and related methods are collectively referred to as "*E. coli* display." In another method, translation of random RNA is halted prior to ribosome release, resulting in a library of polypeptides with their associated RNA still attached. Hereinafter, this and related methods are collectively referred to as "ribosome display."

Other methods employ peptides linked to RNA; for example, PROfusion technology, Phyllos, Inc. See, for example, Roberts & Szostak (1997), Proc. Natl. Acad. Sci. USA, 94: 12297-303. Hereinafter, this and related methods are collectively referred to as "RNA-peptide screening." Chemically

5 derived peptide libraries have been developed in which peptides are immobilized on stable, non-biological materials, such as polyethylene rods or solvent-permeable resins. Another chemically derived peptide library uses photolithography to scan peptides immobilized on glass slides. Hereinafter, these and related methods are collectively referred to as

10 "chemical-peptide screening." Chemical-peptide screening may be advantageous in that it allows use of D-amino acids and other unnatural analogues, as well as non-peptide elements. Both biological and chemical methods are reviewed in Wells & Lowman (1992), Curr. Opin. Biotechnol. 3: 355-62. Conceptually, one may discover peptide mimetics of any

15 protein using phage display, RNA-peptide screening, and the other methods mentioned above.

### Summary of the Invention

The present invention concerns therapeutic agents that modulate the activity of TALL-1. In accordance with the present invention,

20 modulators of TALL-1 may comprise an amino acid sequence  $Dz^2Lz^4$  (SEQ ID NO: 108) wherein  $z^2$  is an amino acid residue and  $z^4$  is threonyl or isoleucyl. Such modulators of TALL-1 comprise molecules of the following formulae:



wherein:

- $a^1, a^2, a^3$  are each independently absent or amino acid residues;
- $a^6$  is an amino acid residue;
- $a^9$  is a basic or hydrophobic residue;
- 30  $a^8$  is threonyl or isoleucyl;

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